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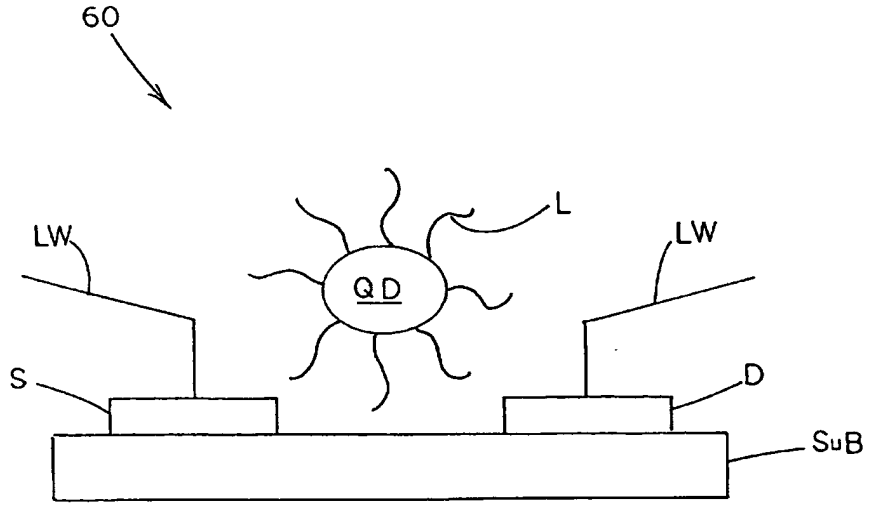
(54) Title: SENSING DEVICES USING CHEMICALLY-GATED SINGLE ELECTRON TRANSISTORS



(57) Abstract: A chemically-gated single-electron transistor (60) having a predetermined current-voltage characteristic and adapted for use as a chemical or biological sensor that is operable at room temperature. The single-electron transistor comprises a substrate (SuB) formed of a first insulating material, source (S) and drain (D) electrodes disposed on the substrate, and a metal nanoparticle (L) disposed between the source and drain electrodes that has a spatial dimension of a magnitude of approximately 12 nm or less. An analyte-specific binding agent is disposed on a surface of the nanoparticle. A binding event occurring between a target analyte and the binding agent causes a detectable change in the current-voltage characteristic.

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Description

SENSING DEVICES USING CHEMICALLY-GATED SINGLE ELECTRON TRANSISTORS

Technical Field

The present invention relates to the electronic sensing, detection and measurement of chemical and biological materials, and specifically relates to sensing devices utilizing single-electron transistors as electronic transducers in conjunction with molecular receptors.

Background Art

The present invention disclosed herein represents, in its broadest sense, an advantageous and practicable conjugation of two distinct fields of inquiry. The first field entails the use of the field effect transistor ("FET") and similar electronic logic devices in the construction of chemical and biological sensing devices. The second field entails the development of the single electron transistor (SET) as an improvement or alternative to the FET as a digital logic element. In order to provide a proper appreciation of the present invention, recent developments in each field will now be described.

One of the most popular types of FETs found in modern digital circuitry is the metal-oxide-semiconductor FET or MOSFET. Two common classes of MOSFETs include n-channel enhancement MOSFETs and n-channel depletion MOSFETs. An enhancement MOSFET, generally designated **10**, is shown in Figure 1A. Highly conductive source and drain regions **S**, **D** contain n-type silicon (*i.e.*, Si with atomic impurities or "dopants" that add excessive free

negative charges), and are separated by an insulating p-type Si channel **12** and substrate **14** (having suitable dopants to add excess free positive charges). A metal electrode known as a gate **G** is provided, and is insulated from substrate **14** by a thin oxide layer **16** (*e.g.*, SiO_2). In the absence of a bias voltage V_{gate} applied between gate **G** and substrate **14**, current cannot flow between source and drain regions **S**, **D** because p-type channel **12** acts as an insulator. In digital electronics, this corresponds to the "OFF" state of the device. Upon application of a positive potential to gate **G**, electrons migrate into the channel **12** and in essence create an n-doped conductive pathway **18** between source **S** and drain **D**; this corresponds to the "ON" state.

The behavior of this "normally off" transistor may be contrasted with that of an n-channel depletion MOSFET shown in Figure 1B, generally designated **20**, in which a thin n-type channel **22** has been inserted under oxide layer **16** between source and drain regions **S**, **D**. In this "normally on" transistor, a conductive path exists between source and drain regions **S**, **D** in the absence of an applied gate bias. When a negative potential is applied to gate **G**, electrons are forced out of channel **22**. This gives channel **22** a p-type (insulating) attribute and eliminates the current path between source and drain regions **S**, **D**. Similar devices, known as p-channel MOSFETs, may be constructed by interchanging then – and p-type materials. Moreover, n-channel and p-channel enhancement MOSFETs may be combined on a single integrated-circuit chip to create a complementary MOSFET or CMOS. Various combinations of CMOS transistors can be used to build the NOT, AND, OR, XOR and other logic gates upon which computer operations are based.

A second important function of the MOSFET is signal amplification. Amplification in a transistor is due to the acceleration of electrons as they move through the strong electric fields in the channel region. This permits signals to propagate through computer circuits without losing their strength.

The important advantages and functions offered by FET technology has led to improvements in the field of chemical and biological sensors or "biosensors." These developments are due in part to the recognition that conventional chemical or biological labeling methods such as the use of radioisotopic, fluorescent, bioluminescent and enzymatic labels, as well as spin labeling, have certain disadvantages. In general, labeling techniques do not possess a high degree of sensitivity and specificity (or selectivity), and are not suitable for miniaturization.

Accordingly, many types of biosensors constructed from conventional FET-type devices have been developed. U.S. Patent No. 4,777,019 to Dandekar is one example of a device that converts a biological chemical signal into an electronic signal to detect or measure a biological material. In the Dandekar device, a biological layer constructed from a mass of semiconductor material (such as silicon nitride or silicon oxide) doped with adenine is provided on the top of the insulated gate layer of an FET. The two hydrogen bond bridges associated with each adenine molecule are able to pair with a thymine molecule, and thus the device may be placed in a solvent to detect the presence and concentration of thymine. The electrostatic field of adenine paired with thymine is different from that of unpaired adenine, and the difference in electrostatic field changes the conductivity in the FET, which in

turn modulates the source and drain current through the FET. In addition, polymers such as poly-Uracil-mRNA could be coupled to the adenine locations to enable the device to detect DNA species in solution.

A FET-based biosensor is also provided in U.S. Patent No. 4,778,769 to Forrest et al. for assaying biologically active substances. A gate insulator formed of a layer of insulating material is disposed on a p-type silicon substrate. The p-type substrate contains two diffusions of n-type silicon to serve as the source and drain areas. A gate electrode is disposed over the gate insulator. A predetermined quantity of an agent, known to be a specific binding partner to the ligand sought to be assayed, is immobilized on the gate electrode. When the gate electrode is at or below the threshold potential (V_T) of the device, there is insignificant flow of electric current between the source and drain areas since no electrons can pass from the n-type source area to the p-type substrate. When the gate electrode potential (V_g) is greater than V_T, an electric field is generated across the gate insulator, which causes repulsion of the majority p-type carriers from the gate insulator/substrate interface, forming a depletion region between the source and drain areas where negative carriers predominate. On applying a voltage potential between the source and drain areas, a drain current will flow.

Another biosensor utilizing the FET as an electronic transducer is disclosed in U.S. Patent No. 4,877,582 to Oda et al. A chemical or biochemical receptor is disposed on the top of the gate of the FET. The receptor comprises immobilized enzymes on membranes, antibodies or microorganisms. In a

specific example, urease immobilized by albumin and glutaraldehyde at the gate is employed to detect the presence of urea.

U.S. Patent No. 4,894,339 to Hanazato et al. also discloses the use of an immobilized enzyme membrane in conjunction with a semiconductor sensor. The enzyme membrane is formed by coating a base with an aqueous solution containing glucose oxidase as the enzyme, a water soluble photosensitive resin containing polyvinyl pyrrolidone and 2,5-bis (4'-azide-2'-sulfobenzal) cyclopentanone sodium salt, and bovine serum albumin. A portion of the dried coating is then irradiated by ultraviolet light to induce photo crosslinking, and treated with glutaraldehyde to induce chemical crosslinking for increased mechanical strength. The sensor is constructed by mounting a hydrogen ion-sensitive insulated gate FET or pH-ISFET chip, which includes two pH-ISFETs, on an epoxy resin board. The enzyme membrane is disposed on one of the pH-ISFETs, and a reference electrode is provided. Electrical leads provide communication with a measuring circuit.

U.S. Patent No. 5,039,390 to Hampp et al. is another example of chemical sensor that includes a chemically sensitive membrane coupled to the gate of an FET. Depending on the membrane selected, the device may be sensitive to ions, gases, enzymes, antibodies/antigens or hydride-forming DNA/RNA groups.

A sensor system capable of simultaneously detecting a wide variety of chemical and biological substances is disclosed in International Publication No. WO 93/08464 (International App. No. PCT/US92/08940). An array of FET-based devices are mounted on a single substrate, along with calibration and

associated circuitry. Each device is provided with a different, specific receptor adapted to measure a different type of substance.

U.S. Patent No. 5,653,939 to Hollis et al. also discloses a system containing an array of FET-based devices, each including a specific probe or receptor adapted to detect a specific target molecule.

FET-based chemical and biological sensors such as those described above have proven useful for a wide variety of applications. Unfortunately, further improvements to their utility as devices for chemical and biological transduction are limited to the same degree as the underlying FET technology. MOSFET devices have dominated computer technologies for several reasons, including their low operating voltages (*e.g.*, 0.1 V), low power consumption, high speed, and the ease with which they have been scaled down in dimension. In the past, MOSFETS could be scaled down simply by shrinking each component part by a constant factor (*i.e.*, the channel, source, gate, leads, *etc.*) and operating the device as usual. As the limits of photolithography are rapidly approached, however, it is becoming clear that continued increases in circuit density will require fairly dramatic changes in the way transistors are designed, fabricated and operated. It is not at all certain that the operating principles of the MOSFET will scale as the size decreases even below 100 nm. As the n-p-n regions in the transistor shrink, their ability to control the flow of electrons is overcome by the quantum mechanical probability that the electrons simply tunnel through the n-p interface. Furthermore, as the transistor density increases the probability that an electron can tunnel between neighboring transistors increases. These tunneling processes cause errors in data

manipulation and storage. There is also concern that as the size of a MOSFET decreases, the ability to make any two transistors with the same electronic properties will be lost (*i.e.*, achieving a specific dopant density in any two devices will be difficult). At the present time, a better approach for many applications is to circumvent the effects of the laws of quantum physics rather than to attempt to capitalize on them.

One such approach has been to develop devices based on single electron nanoelectronics as an alternative to employing bulk current devices for transmitting digital information, although heretofore this approach has been explored only for the purpose of improving methods for processing digital information and not chemical transduction. Of interest is the fabrication of transistors that operate based on the flow of single electrons through nanometer-sized metal or semiconductor particles (also referred to hereinafter as nanoclusters, metal islands, metal dots, or quantum dots), *i.e.*, single electron transistors ("SETs") which operate on the theory of single electron tunneling. An SET is similar in general principle to the conventional FET. However, in an SET a correlated transfer of electrons one-by-one in metallic islands generally occurs when the energy (e^2/C_T, where "e" is the electron charge and C_T is the total island capacitance) required to charge the island by a single electron is large relative to that supplied by thermal energy (kT). Logic operations in the SET thus are based on the tunneling of single electrons through the nanometer-sized dots.

With regard to conventional electronic elements, the discreteness of a single electron charge is not significant at the macroscopic level. For example,

a macroscopic capacitor connected to a battery is charged by displacing electrons from their fixed positively-charged ions on one plate and transferring them through a dielectric material to a second plate. The work required by the battery to perform this operation is given by equation (1):

$$W = q^2/2C$$

where $q = ne$ is the total charge stored, "e" is the charge on a single electron, and C is the capacitance. For a typical computer capacitor having a picofarad (p*F*) capacitance and, for example, an applied voltage potential of 100 mV, the total charge might be one million electrons. Importantly, if the capacitor junction was thin enough and a single electron was able to tunnel from one plate to the other, there would be no observable effect on the charging potential. Thus, although electrons are constrained to integer values once the capacitor is charged, the "granularity" of electrons is not apparent in macroscale devices.

On the other hand, if the junction capacitance is small (< ~ 10^{-18} F) and the resistance is high, the charging energy and tunneling of single electrons in the circuit can affect the current-voltage (*I-V*) characteristics of the capacitor. For example, Figure 2 shows a device consisting of a bulk metal-insulator-nanocluster-insulator-bulk metal double-tunnel junction, or "MINIM" or "MIDIM", generally designated **30**. (For purposes of the present disclosure, the terms "cluster" and "particle" are used interchangeably to describe both semiconductor and metal particles having a diameter less than ~ 50 nm.) In general, a layer **32** of insulating material (which could be a semiconductor) is disposed between two metal regions or electrodes **34**, **36**. A metal

nanoparticle or nanocluster **QD** is disposed on insulating layer **32**. First and second insulating junctions **J1** and **J2** are effectively defined on either side of nanocluster **QD**. When MINIM **30** is biased by an external voltage source V_{ext}, an extremely unusual current response is observed as MINIM **30** or nanocluster capacitor is charged. Current steps are observed and separated by voltage plateaus which may span hundreds of mV, as shown in Figure 4. This response is known as a Coulomb staircase. Each current step corresponds to the addition of a single electron to nanocluster **QD**.

In the semi-classical approach, MINIM **30** is treated as two capacitors with capacitances and resistances C_1, R_1 and C_2, R_2 placed in series and driven by an ideal voltage source, V_{ext}, as shown in Figure 3A. (The term "ideal" is used here to describe a battery with zero internal resistance that can deliver charge instantly.) The state of the system is described by the voltage drop (V_1, V_2) across each junction **J1**, **J2** and Q_0, the number of electrons on nanocluster **QD**. The dynamics of the system are then determined by the probabilities that an electron will tunnel across first junction **J1** and/or second junction **J2**, thus altering Q_0 (*i.e.*, a stochastic approach). These tunneling events are dependent on the change in energy of each electron as it tunnels from bulk metal or electrode **34** through first junction **J1** and onto nanocluster **QD**.

For a better understanding by one skilled in the art, this dependence may be theoretically quantified by considering what happens to MINIM **30** when placed in contact with electrodes **34**, **36** but before an external bias is applied. The Fermi levels of electrodes **34**, **36** and nanocluster **QD** will attempt to align by tunneling electrons from electrodes **34**, **36** to nanocluster **QD**. In general,

the Fermi levels will not be able to align exactly, but will be offset in energy by one or more electrons. This is due to the discrete nature of charge and any impurities present in the junction region. For purposes of reaching a simplified quantification, however, it can be assumed that alignment is perfect and that the quantum mechanical energy levels are closer in energy than the electrostatic energy levels. It should be noted that misalignments in the Fermi level can be accounted for by adding a voltage offset term to equation (8) set forth hereinbelow. Also, the assumption regarding quantum mechanical energy levels is valid for metal particles larger than approximately 5 nm in diameter. Semiconductor particles, however, display quantum effects at sizes much greater than this. Finally, it should be assumed that the resistances of junctions **J1**, **J2** are so large ($R > h/e^2$) that the electrons are localized on one side of a junction or the other side.

When the system is in electrostatic equilibrium, a potential is applied by the voltage source V_{ext} and n electrons tunnel through the thin insulating barrier of junction **J1** and onto nanocluster **QD**. The value n can be found as a function of the applied potential (or applied energy). To describe this process energetically, a localized approach is taken to obtain the quantity $\Delta E_1 = E_f - E_i$, where ΔE_1 is the difference in the energy of junction **J1** before (E_i) and after (E_f) the tunneling of the electron. This quantity represents the energy that must be supplied by external voltage source V_{ext} in order to place an electron on nanocluster **QD**. Referring to Figure 3B, the initial state is the energy of junction **J1** charged by n electrons. This energy is given by equation (2):

$$E_i = (ne)^2/2C_T$$

where "e" is the charge on a single electron and $C_T = C_1 + C_2$ is the total cluster capacitance, *i.e.*, the capacitance an electron "sees" when tunneling across first junction **J1**. The final energy state, E_f, is the energy of the system with an electron on nanocluster **QD**. Placing an electron on nanocluster **QD** lowers the potential across V_1, which causes a polarization charge to flow through the circuit. Consequently, battery V_{ext} does work eV_1 to bring an electron from second electrode **36** to first electrode **34**. When combined with the energy associated with changing the cluster charge by one electron, equation (3) is obtained:

$$E_f = eV_1 + [(Q_0 - e)^2/2C_T]$$

Upon expanding the second term in equation (3) and subtracting equation (2), equation (4) is obtained:

$$E_f - E_i = eV_1 - (Q_0e/C_T) + (e^2/2C_T)$$

The energy of the system is fully described by the change in the cluster charge and the work done by voltage source V_{ext}. To calculate the external voltage that must be applied by a battery or a potentiostat, a relation between V_1 and V_{ext} is needed. First, the law of charge conservation gives equation (5):

$$C_1V_1 = C_2V_2$$

Then, Kirchhoff's loop laws gives equation (6):

$$V_{ext} = V_1 + V_2$$

Combining equations (5) and (6) yields equation (7):

$$V_1 = C_2V_{ext}/C_T$$

and finally equation (8):

$$\Delta E_1 = (eC_2V_{ext}/C_T) - (eQ_0/C_T) + (e^2/2C_T)$$

The first term in equation (8) is the work performed by voltage source V_{ext} to maintain V_1 after an electron has tunneled to nanocluster **QD**. The second and third terms represent the single electron charging effects. The second term is the additional work required to tunnel an electron to nanocluster **QD** if an electron or electrons are already present on nanocluster **QD**. This term provides the voltage feedback necessary to prevent the tunneling of more than *n* electrons to the cluster per voltage increment, where *n* is the step number (*e.g.*, $1e^-$, $2e^-$, *etc.* in Figure 4). In contrast to the macroscale capacitor described above, where the tunneling of a single electron would not be noticed, the transfer of a single electron through a nanoscale capacitor such as device **30** causes a substantial energy change in the circuit. This prevents more than the allowed number of electrons (*n*) from residing on nanocluster **QD** simultaneously.

The current staircase shown in Figure 4 can now be rationalized by considering the allowed voltage change of junction J1, $\Delta V > 0$. If this were not the case, the electron would immediately tunnel back to where it came from. Accordingly, equation (9) holds:

$$V_{ext} > Q_0/C_2 - e/2C_2$$

In the case of an initially neutral nanoparticle ($Q_0 = 0$), an external voltage of $e/2C_2$ is required before current can flow through the circuit. This phenomena is referred to as the Coulomb gap or Coulomb blockade. When this voltage is reached, a single electron tunnels to nanocluster **QD**. The electron does not remain on nanocluster **QD** indefinitely, but quickly tunnels off through the next junction **J2** (at approximately 100 ps, depending on the ratio

R_2C_2/R_1C_1). It does remain long enough, however, to provide the voltage feedback required to prevent additional electrons from tunneling simultaneously to nanocluster **QD**. Thus, a continuous single-electron current of $I = e/2R_2C_T$ flows though the circuit (where the factor e/RC contains units of charge per time). Each additional electron placed on nanocluster **QD** requires a full e/C_2 in voltage. This leads to the overall 1/2, 3/2, 5/2, *etc.* voltage increments in the current staircase in Figure 4 (with each current step after the prior step of magnitude e/R_2C_T).

With respect to the design of MINIM **30**, junction capacitances and resistances must be optimized. Simulated MINIM *I-V* curves show that the sharpest steps are observed for C_2 and $R_2 \gg C_1$ and R_1. As C_2/C_1 and R_2/R_1 approach 1, the zero-current plateau at 0 V remains but the current steps disappear. If *R* and *C* for junctions **J1** and **J2** are equal, the electron will tunnel through both junctions **J1**, **J2** with identical rates. The voltage feedback required to see current steps is thus lost. Unfortunately, since *C* decreases but *R* increases as the junction thickness increases, these ratios can only be optimized by constructing junctions from materials with different dielectric properties.

Thermal effects are another critical design consideration. SETs have been constructed using polycrystalline silicon or polyacetylene as the quantum dot. Such devices have no practicable use because, in order to produce SET phenomena, they must be cooled to about 4 K. To avoid thermally-activated tunneling processes, $e/2C_2 \gg kT$. As T increases the single-electron current steps are gradually washed out and an ohmic response (*i.e.*, a linear *I-V* curve)

is observed. In general, room temperature operation of SETs requires transistor miniaturization down to the molecular level, employing nanoparticles that are less than approximately 12 nm in diameter and preferably less than 10 nm. Such devices are more feasibly constructed using self-assembly methods, *i.e.*, assembly from solution phase by means of chemical interactions as opposed to lithographic systems.

In U.S. Patent No. 5,420,746 to Smith, an SET device operable at room temperature is disclosed, wherein a cluster of pure carbon atoms, fullerene (C_{60}), is provided as the quantum dot. The device consists of a layer of insulating material (such as silicon dioxide) disposed between two conductive layers. One or more fullerenes are disposed in the insulating material. The device is then biased by a battery by connecting leads to the conductive layers. The device performs as a double barrier tunnel structure, wherein the each fullerene is so small that any tunnel currents will experience a Coulomb blockade effect. Under low bias (*i.e.*, below a certain critical threshold voltage), no current will flow because the charging voltage of the fullerene is greater than the bias applied. That is, the Coulomb blockade effect prevents an electron from tunneling through the insulating material toward the fullerene. Once the critical voltage is obtained, one electron leaves the first conductive layer and tunnels though the insulating material into the fullerene, and then exits the fullerene and continues tunneling through the insulating material into the second conductive layer. The charging voltage of two electrons on the fullerene is greater than the charging voltage of a single electron. Therefore, if the voltage applied to the device is maintained above a charging voltage of

a single electron, but below the charging voltage of two electrons, only one electron at a time will be on the fullerene. As a result of this behavior, the device should have a substantially step-wise current-voltage curve (*I-V* characteristic).

In order to emulate the functionality of a MOSFET, a three-terminal SET device having a spatially well-defined MINIM double-tunnel junction can be provided with a gate electrode disposed near the nanoparticle. The flow of single electrons from source to drain can then be controlled by injecting (or removing) single electrons from the nanoparticle through the gate electrode.

Unfortunately, photolithographic techniques for fabricating complex SET structures are limited to minimum size features of only about 100 nm. Likewise, electron beam lithography, while capable of producing features on the order of 5 nm, is expensive, slow and still not readily available. In addition, relatively simple metal evaporation methods can provide metal islands with features down to 10 nm, but the precise placement and dispersity of the metal islands is difficult to control. In contrast to lithography and metal evaporation, wet-chemical synthesis can provide clusters of almost arbitrary size.

Accordingly, the best approach to date for the fabrication of SET devices is self-assembly, defined as the solution-phase, chemically directed organization of material into pre-designed composite structures. Chemically-synthesized nanoparticles offer several advantages as SET components, the most important of which is their small size. Metal and semiconductor nanoparticles can be prepared in solution with average diameters of tens of Ångstroms and larger. Adsorbed or covalently attached ligands can act as

stabilizers against agglomeration and can be used to import chemical functionality to nanoparticles. Importantly, nanoparticles can be immobilized between insulating thin films though electrostatic or covalent attachment chemistries.

An example of a self-assembled SET operable at room temperature is disclosed in U.S. Patent No. 5,646,420 to Yamashita. A lipid bilayer is supported at one outer side by a carbon substrate and at the other outer side by a conductive layer. Each layer of the lipid bilayer symmetrically includes hydrophobic groups oriented on the inside and hydrophilic groups oriented on the outside. Arranged between each layer of the lipid bilayer is a protein material having an α-helix conformation and four GCCC segments of bacteriorhodopsin. The protein material serves as the insulating material. A quantum dot is supported by the protein material; it is made of a conductive organic compound such as Flavin, or 7-acetyl-10-methyl-isoalloxazine wherein the acetyl group is combined to an *s* atom of a cysteine of a G segment of the sequence of the protein material. A pair of electrodes serve as the source and drain, and are made of an inner complex salt such as Mn^{3+} terrakis-tetraphenyl-porphyrin in which each ortho position of four phenyl groups is respectively combined to a corresponding alanine amino group (i.e., the end amino acid) of each segment. The electrodes are respectively combined to the upper and lower ends of the protein material. A polyacetylene control gate (or other organic polymer having a π electron) is disposed between the opposed hydrophobic groups and connected to the quantum dot. Finally, an outer terminal is inserted through a hole in the carbon substrate.

Single electron transfer occurs through the single Flavin molecule due to the tunneling effect. The nearest transition level to the Fermi level is higher than the thermal excitation level (25 mV) of an electron at room temperature, enabling room-temperature SET phenomena. When the outer terminal contacts the control gate, application of a voltage to the control gate causes a variation of potential energy of the Flavin molecule. Increasing the voltage generates additional transition levels for electrical conduction, resulting in step-wise *I-V* characteristics. The disclosure indicates that this device may be useful as a highly miniaturized electronic switch.

Applicants believe that the benefits obtained by the devices exhibiting SET phenomena as described hereinabove have heretofore not been applied to the field of chemical and biological transduction. Therefore, there is a long felt need for SET-based chemical and biological sensors which can take advantage of the increased sensitivity, selectivity, and miniaturization that an SET device can provide. Applicants have discovered such a device, which is described in detail hereinafter.

Disclosure of the Invention

The present invention provides combines one or more chemical and/or biological sensing elements with an SET-based transducer, and can be adapted for use with a wide variety of portable, small-scale sensory systems and applications. A number of advantages are readily apparent from the present disclosure: (i) capability of detecting single molecules, single-molecule binding events, and single-molecule redox reactions; (ii) diminutive dimensions that enable the integration of thousands to millions of sensors on a single chip

or substrate; (iii) fast response times; (iv) selectivity; (v) low cost; and (vi) low power consumption.

Accordingly, a chemically-gated single-electron transistor is provided. The single-electron transistor has a predetermined current-voltage characteristic, is adapted for use as a chemical or biological sensor, and is operable at room temperature. The single-electron transistor comprises a substrate formed of a first insulating material, source and drain electrodes disposed on the substrate, and a metal nanoparticle disposed between the source and drain electrodes and having a spatial dimension of a magnitude of approximately 12 nm or less. An analyte-specific binding agent is disposed on a surface of the nanoparticle. A binding event occurring between a target analyte and the binding agent causes a detectable change in the current-voltage characteristic.

In another embodiment of the invention, a device for sensing chemical or biological substances comprises a single-electron transistor having a predetermined current-voltage characteristic and including an insulated substrate, a source electrode disposed on the substrate, a drain electrode disposed on the substrate, and an array of metal nanoparticles disposed between the source and drain electrodes, with each nanoparticle having a spatial dimension of a magnitude of approximately 12 nm or less. An analyte-specific binding agent is disposed on a surface of each nanoparticle, wherein a binding event occurring between a target analyte and one or more of the nanoparticles causes a detectable change in the current-voltage characteristic.

In another embodiment of the invention, a device for sensing chemical or biological substances comprises a plurality of single-electron transistors having predetermined current-voltage characteristics. Each single-electron transistor includes an insulated substrate, source and drain electrodes disposed on the substrate, and a metal nanoparticle disposed between the source and drain electrodes. Each nanoparticle has a spatial dimension of a magnitude of approximately 12 nm or less. An analyte-specific binding agent is disposed on a surface of each nanoparticle, wherein a binding event occurring between a target analyte and the nanoparticle causes a detectable change in the current-voltage characteristic. A voltage source communicates with the single-electron transistors, and an integrated circuit communicates with the single-electron transistor. The integrated circuit is adapted to interpret changes in the current-voltage characteristics of the single-electron transistors caused by the occurrence of a binding events.

In another embodiment of the invention, a device for sensing chemical or biological substances comprises an insulated substrate, a plurality of elongated lower electrodes disposed on the substrate in spaced intervals from each other, and a plurality of elongated upper electrodes disposed transversely above the lower electrodes in spaced intervals from each other. The upper and lower electrodes cooperatively form a grid pattern that includes a plurality of regions of intersection between the upper and lower electrodes, with each region of intersection defining a test site. A single-electron transistor is constructed at each test site. Each single-electron transistor has a pre-established reference current-voltage characteristic and includes a metal

nanoparticle disposed between the upper and lower electrodes at each test site. Each nanoparticle has a spatial dimension of a magnitude of approximately 12 nm or less and is stabilized by an insulating medium. Each nanoparticle has an analyte-specific binding agent disposed on a surface of each nanoparticle, wherein a binding event occurring between a target analyte and the nanoparticle causes a detectable change in the current-voltage characteristic of the nanoparticle. A voltage source communicates with the upper and lower electrodes. An integrated circuit communicates with the test sites and is adapted to interpret changes in the current-voltage characteristics of the single-electron transistors caused by the occurrence of binding events.

In another embodiment of the invention, a chemically-gated single-electron transistor has a predetermined current-voltage characteristic, is adapted for use as a chemical or biological sensor, and is operable at room temperature. The single-electron transistor comprises a lower insulating substrate, an intermediate metal layer disposed on the lower insulating substrate, and an upper insulating substrate. A well is formed in the upper insulating substrate and the intermediate metal layer, and defines a source electrode in a first portion of the intermediate metal layer and a drain electrode in a second portion of the intermediate metal layer. An upper metal layer is disposed on the upper insulating substrate and over the well. A metal nanoparticle is disposed within the well, has a spatial dimension of a magnitude of approximately 12 nm or less, and is stabilized within an insulating medium. A molecular receptor is attached to a surface of the upper metal layer, wherein

a binding event occurring between a target analyte and the molecular receptor causes a detectable change in the current-voltage characteristic.

In still another embodiment of the invention, a single-electron transistor probe is adapted to scan a surface for the presence of chemical or biological substances, and comprises a conductive probe tip, a metal nanoparticle having a spatial dimension of 12 nm or less and attached to the probe tip through an insulating medium, and an analyte-specific binding agent attached to the nanoparticle. A binding event occurring between a target analyte and the binding agent causes a detectable change in the current-voltage characteristic.

In still another embodiment of the invention, a single-electron transistor device operable at room temperature and having a predetermined current-voltage characteristic is useful for sensing chemical substances. The single-electron transistor comprises a substrate formed of a first insulating material, a layer of metal disposed on the substrate, and an insulator defining a double tunnel junction. The insulator is formed in a region of the metal layer and includes an oxide of the metal layer, wherein the insulator divides the metal layer into a first region, a second region, and a third region. The first region defines a source electrode, the second region defines a drain electrode, and the third region defines a metal nanoparticle having a spatial dimension of approximately 12 nm or less. Binding of a target molecule to the nanoparticle causes a detectable change in the current-voltage characteristic.

It is therefore an object of the present invention to provide a chemical or biological sensing device that operates under the principles of single-electron transfer.

It is another object of the present invention to integrate the advantages gained from the use of molecular receptors or analyte-specific binding agents found in field-effect transistor-based devices into practical and operable single-electron transistor-based devices.

It is a further object of the present invention to provide a gate for a transistor that is constructed from a metal nanoparticle and modified with a chemical or biological binding agent.

Some of the objects of the invention having been stated hereinabove, other objects will become evident as the description proceeds, when taken in connection with the accompanying drawings as best described hereinbelow.

Brief Description of the Drawings

Figures 1A and 1B are perspective views of conventional field-effect transistors;

Figure 2 is a top plan view of a single-electron transistor;

Figures 3A and 3B are electrical schematics illustrating the operation of the single-electron transistor of Figure 2;

Figure 4 is a plot of current vs. voltage illustrating the electrical response of the single-electron transistor of Figure 2;

Figure 5 is a schematic diagram of the apparatus used to measure the electrical response of a gold nanoparticle stabilized with octanethiol ligands;

Figures 6A and 6B are plots of current vs. voltage illustrating the electrical response of the gold nanoparticle of Figure 5 for different pH values;

Figure 7 is a schematic diagram of the apparatus used to measure the electrical response of a gold nanoparticle stabilized with galvinol ligands;

Figure 8 is a chemical diagram illustrating the conversion of galvinol into galvinoxide;

Figures 9A-9D are plots of current vs. voltage illustrating the electrical response of the gold nanoparticle of Figure 7 for different pH values;

Figure 10 is a side elevational view of a single-electron transistor according to the present invention;

Figure 11 is a side elevational view of another single-electron transistor according to the present invention;

Figures 12A and 12B are plots of current vs. voltage illustrating the electrical response of the single-electron transistor of Figure 11 when operating in amperometric mode and potentiometric mode, respectively;

Figure 13 is a diagrammatic view illustrating an example of the operation of the single-electron transistor of Figure 11;

Figures 14A and 14B are exemplary plots of current vs. voltage and current vs. time, respectively, illustrating the behavior of the single-electron transistor of Figure 11 when operating as shown in Figure 13;

Figure 15 is a schematic view of a single-electron transistor including an array of nanoparticles according to the present invention;

Figure 16 is a top plan view of a biochemical sensing device including a plurality of single-electron transistors according to the present invention;

Figure 17A is a perspective view of a biochemical sensing device including a plurality of single-electron transistors arranged in a grid-like pattern of test sites according to the present invention;

Figure 17B is a detailed side elevational view of a test site of the device of Figure 17A;

Figure 18 is a side elevation view of another single-electron transistor according to the present invention;

Figure 19 is a perspective view of a single-electron transistor-based scanning probe according to the present invention; and

Figure 20 is a perspective view of another single-electron transistor according to the present invention.

Detailed Description of the Invention

Referring now to the drawings, applicants note that when a gate electrode is attached to an SET device, the current behavior of the device can be altered dramatically by injecting (or removing) a single electron onto the nanoparticle. In other words, the *I-V* curve of an SET device is extremely sensitive to the charge placed on the nanoparticle by an outside source. If a single electron is injected onto the nanoparticle from a gate electrode, the current flowing through the SET device may change by hundreds of picoamps (pA).

Applicants have discovered that the same current sensitivity of the SET device can be achieved by means of a chemical gating mechanism, to create a chemical SET device. Embodiments of the chemical SET device, examples of which are described below, are sensitive to the presence of single analyte molecules that bind to the insulator or nanoparticle surface. The chemical SET device can be made selective by introducing a variety of analyte-specific

binding agents to its surface or to its ligand-capped surface, including self-assembled monolayers, proteins, DNA, inorganics, *etc.*

A significant challenge to incorporating single-electron devices into nanoscale electronic circuitry is the sensitivity of SET currents to impurities which may reside on or near the nanoparticle. Impurities introduce shifts in SET current-voltage curves, making it unlikely that any two SET devices will be electronically equivalent. It has been discovered that particle-capping ligands may be employed as "chemical gates" in order to manipulate SET currents. If, however, it is determined that the nanoparticle selected for use in an SET-based sensor needs to be stabilized by ligand capping, it must further be determined whether the resulting capped nanoparticle is sensitive to physical changes of interest to the chemical sensor industry, or whether an analyte-specific binding agent or molecular receptor may be attached to the capping material.

The results of an exemplary analysis of the invention are illustrated in Figures 5-9. Ligand-stabilized gold (Au) nanoclusters were observed in aqueous solutions. Two different ligands were considered: octanethiol (C_8-Au; 5 nm diameter), and galvinol (Gal-Au; 3 nm diameter) having pK_a ~ 12 when bound to Au nanoclusters. In Figure 5, a gold nanocluster **42** is capped with octanethiol ligands **44** and disposed over a planar Au substrate **46** insulated with an octanethiol coating **48**. In Figure 7, gold nanocluster **42** is capped with galvinol ligands **52**. Individual nanoclusters **42** were probed electronically with a scanning tunneling microscope **54** ("STM") with an insulated (polyethylene) tip **56**. Clear *I-V* steps (Coulomb staircase curves) were observed for C_8-Au in

water (pH 5 and 12) and Gal-Au in water (pH 5, 8, 10, and 12), as respectively shown in Figures 6A and 6B, and 9A, 9B, 9C and 9D. These current steps and voltage plateaus are indicative of SET activity.

Because there is no chemical difference in C_8-Au at the two pH values tested, little change in *I-V* behavior as a function of pH resulted. Voltage plateau widths (ΔV) were 59 ± 7.8 mV and 63 ± 4.6 mV at pHs 5 and 12, respectively. The ΔV value can be used to estimate cluster capacitance using $\Delta V = e/C$, giving capacitances of approximately 2.7 ± 0.30 a*F*/cluster and 2.5 ± 0.10 a*F*/cluster (0.05 a*F*/nm^2). Galvinol, however, is converted to the galvinoxide anion as pH is increased as shown in Figure 8. Thus, changes in *I-V* behavior occurred for Gal-Au in response to deprotonation. A subtle shift (approximately 30 mV) in the entire staircase (the *I-V* curve) to positive bias potentials is noticeable from pH 5 to pH 8. The shift is even more prevalent in the *I-V* curves obtained at pHs 10 and 12 (from approximately 60 to 120 mV). Moreover, ΔV decreases in magnitude from 74 ± 7.8 mV at pH 5 to 64 ± 4.0 mV at pH 8 and to 48 ± 5.6 mV at pH 12.

The chemically induced changes in the SET staircases described above may be rationalized by considering the effects of charge and/or structural changes occurring in the galvinol monolayer upon deprotonation. At pH 5, galvinol is in a protonated neutral form. Coulomb staircases of Gal-Au at pH 5 are therefore typically symmetrical, with the first step centered near 0 V (the Coulomb gap). As the pH is increased, galvinol is converted to galvinoxide anion. The increased negative charge on the nanocluster has two consequences. First, the total capacitance of the cluster increases. Based on

ΔV, an increase in nanocluster capacitance from 2.2 ± 0.24 a*F*/cluster (0.06 a*F*/nm^2) at pH 5 to 2.5 ± 0.14 a*F*/cluster (0.09 a*F*/nm^2) and 3.3 ± 0.31 a*F*/cluster (0.12 a*F*/nm^2) at pHs 8 and 12, respectively, was calculated. The second consequence is an increase negative charge on the nanocluster surface. In solid-state SET devices, negative charge located near the metal island, either from an impurity or through application of a gate electrode bias, causes the Coulomb staircase to shift to positive bias potentials. The shift to positive bias in the Gal-Au system is qualitatively in accord with solid-state measurements. The fact that potential shifts and capacitance changes are only observed for Gal-Au and not C_8-Au, and for Gal-Au at three different pHs of identical ionic strength, demonstrates the feasibility of a pH-gated SET device.

Accordingly, a SET device for directly measuring the pH value of a solution, and for detecting redox events or analyte binding events known to occur as consequence of a change in pH value, is constructed by applicants as shown in Figure 10 and generally designated **60**. Source and drain electrodes **S**, **D** are disposed in a spaced-apart relationship on a surface of a supporting substrate **SUB**. Supporting substrate **SUB** is formed of a normally insulating material such as silicon, silicon dioxide, or polymer. Alternatively, substrate **SUB** could be made of a conductive material and insulated by an insulating material such as a thiol layer. A nanoscopic quantity of metal such as gold, silver or platinum is disposed between source and drain electrodes **S**, **D** to serve as the metal island or nanoparticle **QD.** Nanoparticle **QD** is capped with a ligand substance **L** known to be responsive to pH changes such as a

thiol, and preferably galvinol. Suitable lead wires **LW** or the like are then connected to source and drain electrodes. A change in the pH value of a solution in contact with the device will cause a shift in the stepwise *I-V* curve in the manner described above. This change may be accurately measured and interpreted with the aid of circuitry or other known means.

An SET-based, chemically-gated sensor device, generally designated **70**, having a base construction similar to pH-gated SET device **60** may be utilized as a transduction element in a wide variety of sensors or test sites designed with different types of chemical gates to selectively detect a particular analyte, *i.e.*, a target molecule, chemical compound, or biological material. Applicants have accomplished this by attaching an analyte-specific binding agent or molecular receptor **A** either directly to nanoparticle **QD** or to capping ligand or **I** (which serves as the double-tunnel junction). Depending on the particular binding agent chosen, a measurable change in the *I-V* characteristics will occur in SET device **70** in the event that an analyte **B** binds to binding agent **A**. In such a configuration, capping ligand or insulator **I** functions as a double-tunnel junction and binding agent **A** functions as a chemical gate electrode for SET device **70**. A wide variety of binding agents **A** may be chosen, including self-assembled monolayers, proteins, antibodies/antigens, DNA, and inorganics. And, consequently a wide variety of analytes **B** may be detected according to known binding relationships and chemistry.

Both amperometric and potentiometric modes of operation are possible for sensor device **70**, as shown respectively in Figures 12A and 12B. The solid

lines represent the *I-V* curve of sensor device **70** in the absence of analyte **B**, and the dashed lines represent the curve in the presence of analyte **B**.

In amperometric mode, the source-drain potential will be biased at a point on any arbitrary voltage plateau on the *I-V* curve, such as by employing a battery or potentiostat. When analyte **B** binds to nanocluster **QD**, the charge on nanocluster **QD** will change and consequently alter the *I-V* properties of sensor device **70**, effectively shifting the entire *I-V* curve up or down in current by one electron, as shown by the dashed line in Figure 12A. Since the bias voltage is fixed by a potentiostat (V_{hold}), the current flowing through the circuit must change by ± *n*e, where *n* is the number of charges injected into (+e) or removed from (-e) nanocluster **QD**. In other words, sensor device **70** must remain on the same current step following charge injection (or removal), and the only parameter that is allowed to change is the current. The change in nanocluster charge thus causes current to flow (or not to flow, depending on the configuration or bias of sensor device **70**), such that sensor device **70** in effect has a "chemical" gate.

In potentiometric mode, illustrated in Figure 12B, a fixed current is forced through the junction between source **S** and drain **D** and the potential across the junction is monitored. In this case, since the current is fixed (I_{hold}), the potential must change in order to maintain a fixed position of the current step. In fact, large changes in potential (approximately 200 mV for a 10-nm diameter nanocluster) can be expected in response to the addition of a single charge to nanocluster **QD**.

In either case, because the *I-V* curve of sensor device **70** is sensitive to mere $1e^-$ changes in charge injected onto nanocluster **QD**, single-molecule analytes can be detected. Moreover, because signal transduction is based on the transfer of a single electron, response times on the order of 10^{-12} are possible.

Figure 13 is a diagrammatic representation of applicants' sensor device **70**, configured such that a single-electron flow between metal leads occurs across nanocluster **QD** in the absence of a molecular binding event. When target analyte **B** binds to molecular recognition element **A**, the gate "closes" and the shift in *I-V* response shown in Figure 14A may be detected. Figure 14B is a corresponding plot of current as a function of time, and illustrates that the operation of sensor device **70** can be advantageously employed as digital information.

A number of embodiments may be constructed from the novel device described above. For instance, in Figure 15 an array of nanoparticles or cluster array **80** is provided between source and drain electrodes **S**, **D** in order to increase the area of the testing site and improve the chances of detecting the desired analyte, or to measure the concentration of the analyte in solution. Cluster array **80** may be electrically connected to an external voltage source **V** and an integrated analysis circuit **IC** for interpreting changes in *I-V* characteristics.

In addition, a test card or wearable badge, generally designated **90**, may be provided as shown in Figure 16. Wearable badge **90** includes an integrated analysis circuit **IC**, a source potential such as a watch battery **WB**, and a

plurality of sensing cluster arrays **80**. Individual sensing arrays **80** or groups thereof may include different binding agents attached to their respective nanoparticles or capping ligands, such that wearable badge **90** is able to detect a variety of different analytes. Known methods may be employed to enable integrated analysis circuit **IC** to discriminate among the various signals received from different sensing arrays **80**. For example, the location of each individual sensing array **80**, and the identification of its binding agent or the corresponding analyte to be detected by that particular sensing array **80**, may be digitized. Thus, a change in the *I-V* characteristic of a particular sensing array **80**, such as the presence or absence of a signal from that sensing array **80**, could be interpreted by integrated analysis circuit **IC** as a positive test for the presence of the analyte known to bind to the receptor associated with that sensing array **80**.

In Figure 17A, an array is provided in the configuration of a conductive sandwich grid, generally designated **100**. A plurality of top electrodes **TE** are disposed in orthogonal relationship to a plurality of bottom electrodes **BE** to form conductive grid **100**. Each location where electrodes **TE** and **BE** cross defines a test site **TS**. A plurality of nanoparticles **QD** are interposed between electrodes **TE**, **BE** at each test site **TS**. As shown in the detailed view of Figure 17B, an insulating material **I** such as a plurality of ligands is provided to serve as the double-tunnel junction. At each test site **TS**, one of electrodes **TE** or **BE** serves as the source electrode while the other serves as the drain electrode. Accordingly, each test site **TS** effectively contains a single SET transistor. Each transistor or group of transistors may contain different binding agents, so

that conductive grid **100** may contain a number of test sites **TS** designed to detect a number of different analytes.

In Figure 18, a back-gated SET transistor is provided by applicants, generally designated **110**. Source and drain electrodes **S**, **D** are sandwiched between upper and lower insulating substrates **112**, **114**. A nanoparticle **QD** and capping ligand or other insulating material **I** are disposed in a well **116** formed between source and drain electrodes **S**, **D**. A metal layer **118** is disposed above nanoparticle **QD** to form the base of the chemical gate of SET transistor **110**. A plurality of molecular recognition elements **A** are attached to metal layer **118**, thereby increasing the sensitivity of SET transistor **110** to a binding event with target analyte **B**. As in the other embodiments disclosed herein, the presence of non-target species **C** have no effect on the *I-V* characteristics of SET transistor **110**.

In Figure 19, an SET probe **120** is provided by applicants to enable the scanning of a test surface **122**. A nanoparticle **QD** is attached by means of a suitable ligand **L** to a probe tip **124**. Probe tip **124** may be a platinum-iridium (Pr-Ir) tip. The magnitude of the change in *I-V* characteristics of SET probe **120** will depend upon the existence of certain molecules or radicals present on test surface **122**. For example, the response of probe tip **120** in the presence of methane (CH_3) will differ from the response in the presence of hydroxide (OH). Using known calibration data, a surface scan performed by probe tip **120** will generate information which may be rasterized to produce an image indicative of the chemical signature of test surface **122**. A molecular receptor

may be attached to either nanoparticle **QD** or ligand **L** in order to scan for a particular substance.

In some cases, applicants have found that an SET-based chemical sensor may be constructed with a gate which does require an additional analyte-specific binding agent for its successful operation. The pH-gated sensor **60** in Figure 10 is one example. Another example is the embodiment illustrated in Figure 20, which may be used as a carbon monoxide (CO) detector, generally designated **130**. A layer **132** of platinum (e.g., 5 nm) is deposited on an insulating substrate **SUB** such as n-type silicon. Thin lines of platinum (approximately 1 nm x 10 nm x 5 nm deep) are oxidized to platinum oxide (PtO) in an aqueous/H_2SO_4 medium using the tip of an STM in order to define an isolated platinum island **QD** (*i.e.*, the metal or quantum dot). As a result, a Pt-PtO-Pt nanoparticle-PtO-Pt double-tunnel junction J is formed, with outer metal regions serving as the source and drain electrodes **S**, **D**. CO detector **130** is sensitive to the presence of CO because Pt-CO adsorption occurs at Pt island **QD**, thereby altering the *I-V* characteristic of this SET transistor. Similar sensors may be constructed by generalizing this approach; that is, several different metal/metal-oxide combinations are possible which are known to bind small molecules of interest in chemical sensing (Ti and Sn, for example).

It will thus be seen that there is provided, as described hereinbefore, an electronic device for sensing chemical and/or biological substances, wherein the transducer element operates according to single-electron transfer phenomena and is highly responsive to molecular binding events. The device

can be constructed by means of self-assembly methods, is extremely small, and consumes a very low amount of power. The sensitivity, selectivity, accuracy and other properties of this SET-based device are superior to conventional FET-based devices. A very large number of these devices can be integrated into a single chip or substrate and utilized in connection with a wide variety of sensing systems.

It will be understood that various details of the invention may be changed without departing from the scope of the invention. Furthermore, the foregoing description is for the purpose of illustration only, and not for the purpose of limitation--the invention being defined by the claims.

CLAIMS

What is claimed is:

1. A chemically-gated single-electron transistor having a predetermined current-voltage characteristic and adapted for use as a chemical or biological sensor operable at room temperature, comprising:

(a) a substrate formed of a first insulating material;

(b) a source electrode disposed on the substrate;

(c) a drain electrode disposed on the substrate;

(c) a metal nanoparticle disposed between the source and drain electrodes and having a spatial dimension of a magnitude of approximately 12 nm or less; and

(d) an analyte-specific binding agent disposed on a surface of the nanoparticle, wherein a binding event occurring between a target analyte and the binding agent causes a detectable change in the current-voltage characteristic.

2. The single-electron transistor according to claim 1 further comprising a second insulating material attached to the surface of the nanoparticle, and wherein the analyte-specific binding agent is attached to the second insulating material.

3. The single-electron transistor according to claim 1 wherein the nanoparticle has a spatial dimension of a magnitude of approximately 10 nm or less.

4. The single-electron transistor according to claim 1 wherein the nanoparticle is formed of gold.

5. The single-electron transistor according to claim 1 wherein the nanoparticle is formed of silver.

6. The single-electron transistor according to claim 1 wherein the nanoparticle is formed of platinum.

7. The single-electron transistor according to claim 1 further comprising a voltage source adapted to apply a fixed bias potential, wherein a binding event occurring between a target analyte and the binding agent causes a substantially step-wise change in current flowing through the transistor.

8. The single-electron transistor according to claim 1 further comprising a current source adapted to apply a fixed current, wherein a binding event occurring between a target analyte and the binding agent causes a substantially step-wise change in voltage between the nanoparticle and the electrodes.

9. A device for sensing chemical or biological substances comprising a single-electron transistor having a predetermined current-voltage characteristic and including an insulated substrate, a source electrode disposed on the substrate, a drain electrode disposed on the substrate, an array of metal nanoparticles disposed between the source and drain electrodes, each nanoparticle having a spatial dimension of a magnitude of approximately 12 nm or less, and an analyte-specific binding agent disposed on a surface of each nanoparticle, wherein a binding event occurring between a target analyte and one or more of the nanoparticles causes a detectable change in the current-voltage characteristic.

10. The device according to claim 9 further comprising a voltage source coupled to the source and drain electrodes and an integrated circuit communicating with the single-electron transistor and adapted to interpret the change in the current-voltage characteristic of the single-electron transistor caused by the occurrence of a binding event.

11. The device according to claim 9 further comprising an insulating medium attached to the nanoparticles.

12. The device according to claim 11 wherein the binding agents are attached to portions of the insulating medium corresponding to each nanoparticle.

13. A device for sensing chemical or biological substances comprising:

(a) a plurality of single-electron transistors having predetermined current-voltage characteristics, each single-electron transistor including an insulated substrate, a source electrode disposed on the substrate, a drain electrode disposed on the substrate, a metal nanoparticle disposed between the source and drain electrodes, each nanoparticle having a spatial dimension of a magnitude of approximately 12 nm or less, and an analyte-specific binding agent disposed on a surface of each nanoparticle, wherein a binding event occurring between a target analyte and the nanoparticle causes a detectable change in the current-voltage characteristic;

(b) a voltage source communicating with the single-electron transistors; and

(c) an integrated circuit communicating with the single-electron transistor and adapted to interpret changes in the current-voltage characteristics of the single-electron transistors caused by the occurrence of a binding events.

14. The device according to claim 13 further comprising an insulating material attached to the surface of each nanoparticle, and wherein the analyte-specific binding agent is attached to the insulating material.

15. The device according to claim 13 wherein each single-electron transistor includes a plurality of nanoparticles arranged in an array between the source and drain electrodes.

16. The device according to claim 13 wherein each single-electron transistor includes a binding agent different from the binding agents of the other single-electron transistors, each binding agent being adapted to receive a different target analyte, and wherein the integrated circuit is adapted to interpret a change in the current-voltage characteristic of each single-electron transistor, and to discriminate between responses of each single-electron transistor, based on a predetermined reference current-voltage characteristic and address for each single-electron transistor.

17. The device according to claim 13 wherein the plurality of single-electron transistors are divided into a plurality of groups of single-electron transistors, the single-electron transistors of each group including a binding agent different from the binding agents of the single-electron transistors of the

other groups and adapted to detect a different target analyte, and wherein the integrated circuit is adapted to interpret a change in the current-voltage characteristic of the single-electron transistors of each group, and to discriminate between responses of the single-electron transistors of each group, based on a predetermined reference current-voltage characteristic and address for the single-electron transistors of each group.

18. A device for sensing chemical or biological substances comprising:

(a) an insulated substrate;

(b) a plurality of elongated lower electrodes disposed on the substrate in spaced intervals from each other;

(c) a plurality of elongated upper electrodes disposed transversely above the lower electrodes in spaced intervals from each other, the upper and lower electrodes cooperatively forming a grid pattern including a plurality of regions of intersection between the upper and lower electrodes, each region of intersection defining a test site;

(d) a single-electron transistor constructed at each test site, each single-electron transistor having a pre-established reference current-voltage characteristic and including a metal nanoparticle disposed between the upper and lower electrodes at each test site, each nanoparticle having a spatial dimension of a magnitude of approximately 12 nm or less and stabilized by an insulating medium, and each nanoparticle having an analyte-

specific binding agent disposed on a surface of each nanoparticle, wherein a binding event occurring between a target analyte and the nanoparticle causes a detectable change in the current-voltage characteristic of the nanoparticle;

(b) a voltage source communicating with the upper and lower electrodes; and

(c) an integrated circuit communicating with the test sites and adapted to interpret changes in the current-voltage characteristics of the single-electron transistors caused by the occurrence of binding events.

19. The device according to claim 18 wherein the binding agent of each single-electron transistor is attached to the insulating medium.

20. The device according to claim 18 wherein each single-electron transistor includes a binding agent different from the binding agents of the other single-electron transistors, each binding agent being adapted to receive a different target analyte, and wherein the integrated circuit is adapted to interpret a change in the current-voltage characteristic of each single-electron transistor, and to discriminate between responses of each single-electron transistor, based on a predetermined reference current-voltage characteristic and address for each single-electron transistor.

21. The device according to claim 18 wherein the test sites are divided into a plurality of groups of test sites, the single-electron transistors of each group of test sites including a binding agent different from the binding agents of the single-electron transistors of the other groups and adapted to

detect a different target analyte, and wherein the integrated circuit is adapted to interpret a change in the current-voltage characteristic of the single-electron transistors of each group, and to discriminate between responses of the single-electron transistors of each group, based on a predetermined reference current-voltage characteristic and address for the single-electron transistors of each group.

22. A chemically-gated single-electron transistor having a predetermined current-voltage characteristic and adapted for use as a chemical or biological sensor operable at room temperature, comprising:

(a) a lower insulating substrate;

(b) an intermediate metal layer disposed on the lower insulating substrate;

(c) an upper insulating substrate, wherein a well is formed in the upper insulating substrate and the intermediate metal layer, the well defining a source electrode in a first portion of the intermediate metal layer and a drain electrode in a second portion of the intermediate metal layer;

(d) an upper metal layer disposed on the upper insulating substrate and over the well;

(e) a metal nanoparticle disposed within the well and having a spatial dimension of a magnitude of approximately 12 nm or less, and stabilized within an insulating medium; and

(f) a molecular receptor attached to a surface of the upper metal layer, wherein a binding event occurring between a target analyte

and the molecular receptor causes a detectable change in the current-voltage characteristic.

23. The single-electron transistor according to claim 22 further comprising a plurality of molecular receptors attached to the surface of the upper metal layer.

24. A single-electron transistor probe adapted to scan a surface for the presence of chemical or biological substances, comprising:

(a) a conductive probe tip;

(b) a metal nanoparticle having a spatial dimension of 12 nm or less and attached to the probe tip through an insulating medium; and

(c) an analyte-specific binding agent attached to the nanoparticle, wherein a binding event occurring between a target analyte and the binding agent causes a detectable change in the current-voltage characteristic.

25. A single-electron transistor device operable at room temperature and having a predetermined current-voltage characteristic useful for sensing chemical substances comprising:

(a) a substrate formed of a first insulating material;

(b) a layer of metal disposed on the substrate;

(c) an insulator defining a double tunnel junction, the insulator formed in a region of the metal layer and including an oxide of the metal layer, wherein the insulator divides the metal layer into a first region, a second region, and a third region, the first region defining a source electrode, the second region defining a drain

electrode, and the third region defining a metal nanoparticle, the nanoparticle having a spatial dimension of approximately 12 nm or less, wherein binding of a target molecule to the nanoparticle causes a detectable change in the current-voltage characteristic.

26. The single electron transistor according to claim 25 wherein the metal layer is platinum and the insulator includes platinum oxide, and wherein adsorption of carbon monoxide at the nanoparticle causes a detectable change in the current-voltage characteristic.

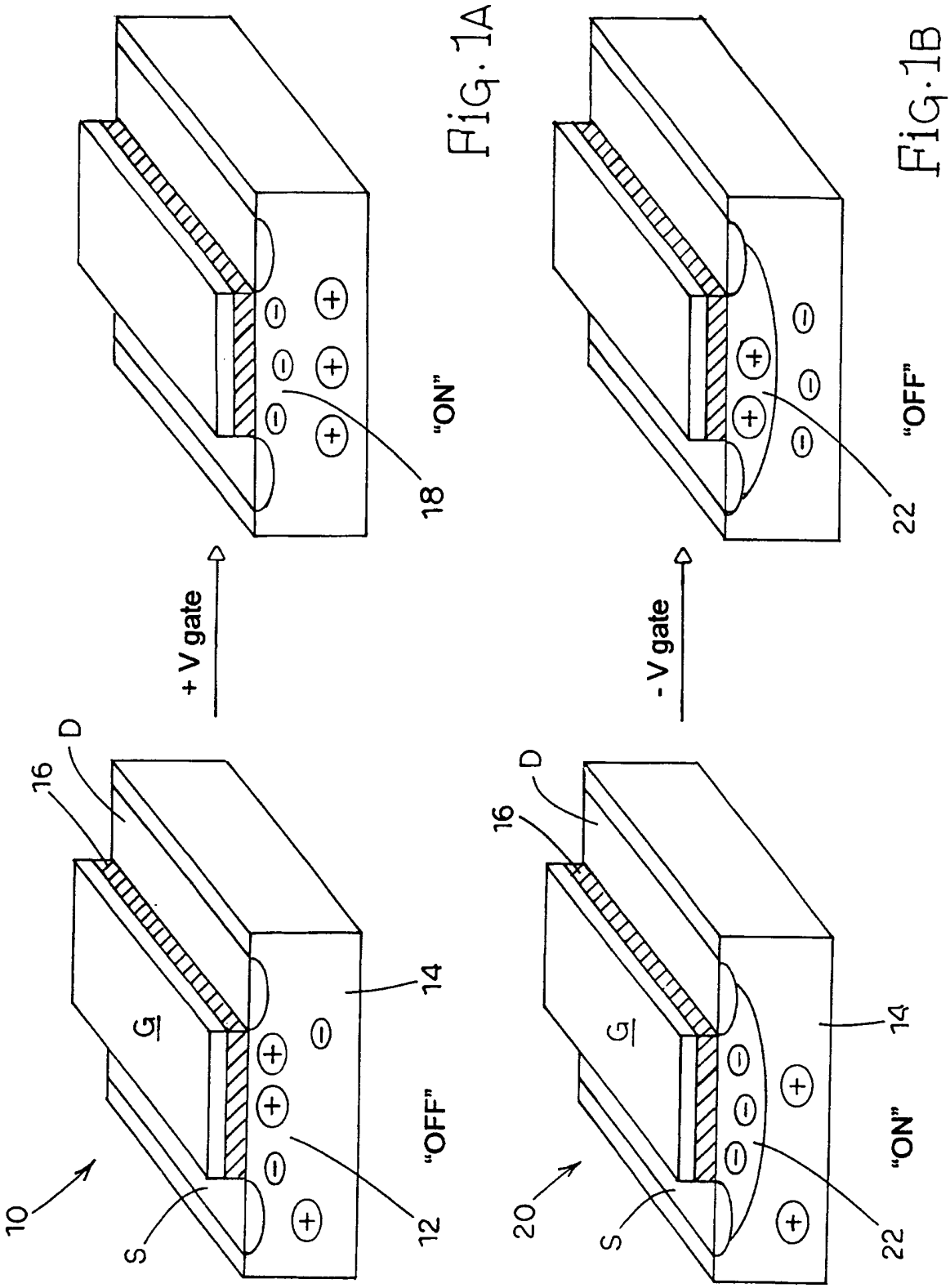

FIG. 1A

FIG. 1B

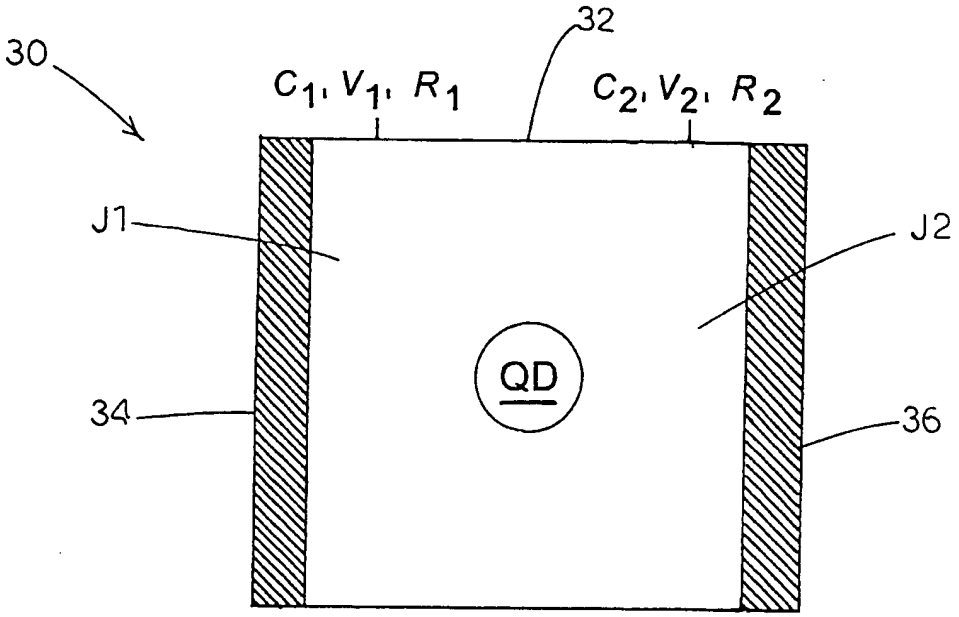

Fig. 2

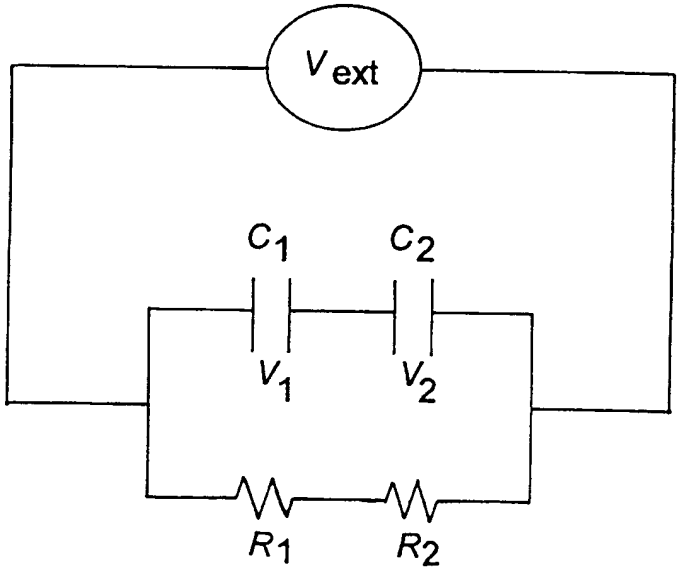

Fig. 3A

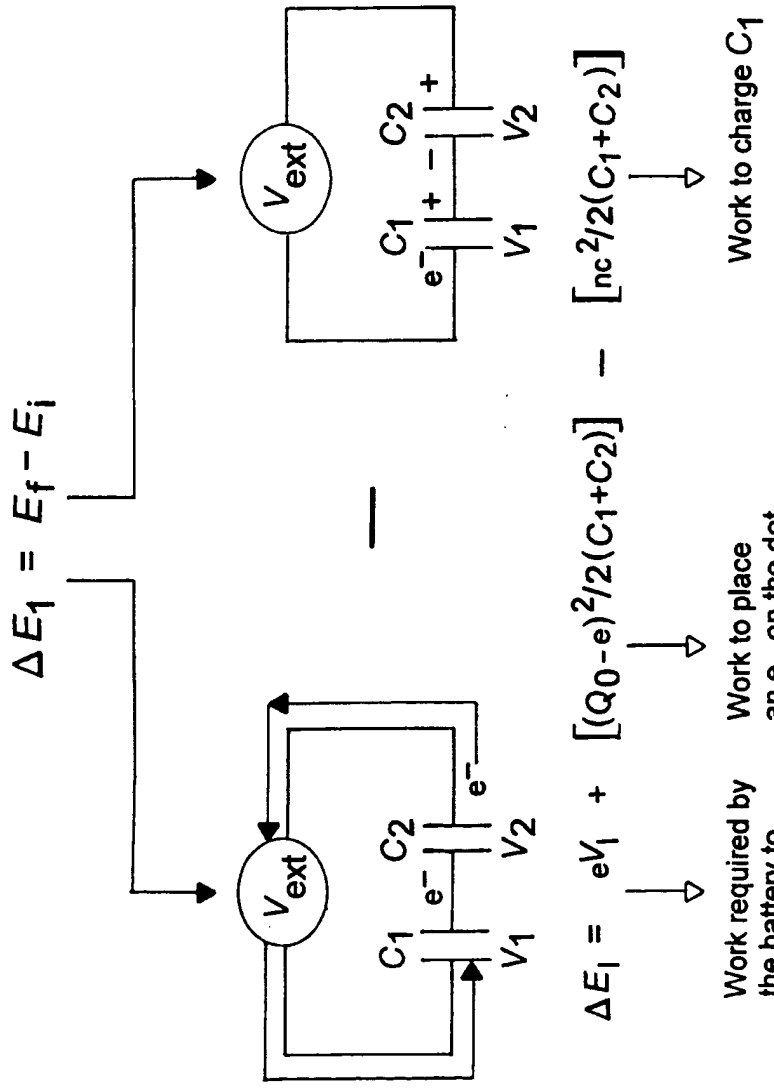
$\Delta E_1 = E_f - E_i$
V_{ext}
C_1
C_2
V_1
V_2
e^-
$\Delta E_1 = eV_1 + [(Q_0-e)^2/2(C_1+C_2)] - [nc^2/2(C_1+C_2)]$
Work required by the battery to maintain V_1
Work to place an e on the dot in the presence of ne's on the dot
Work to charge C_1

FIG. 3B

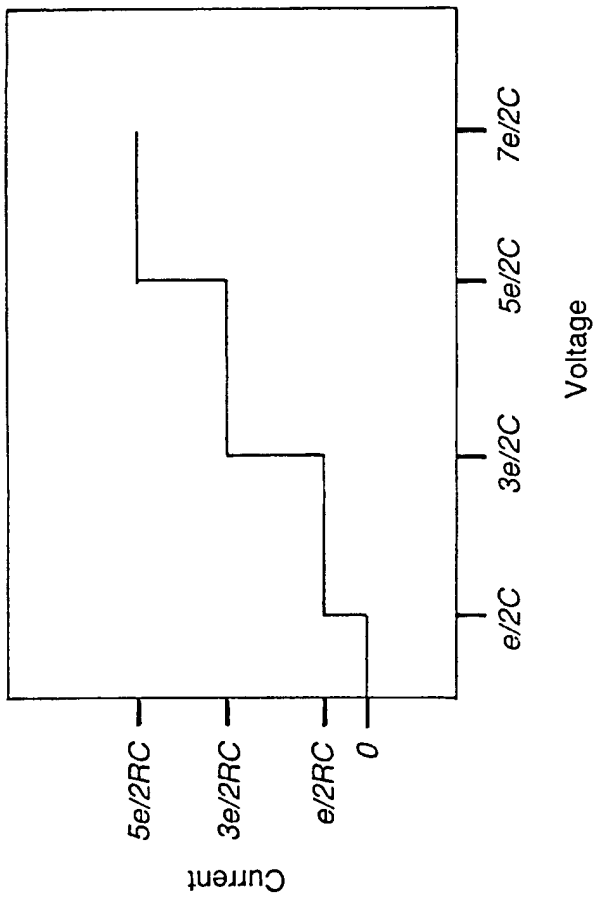

FIG. 4

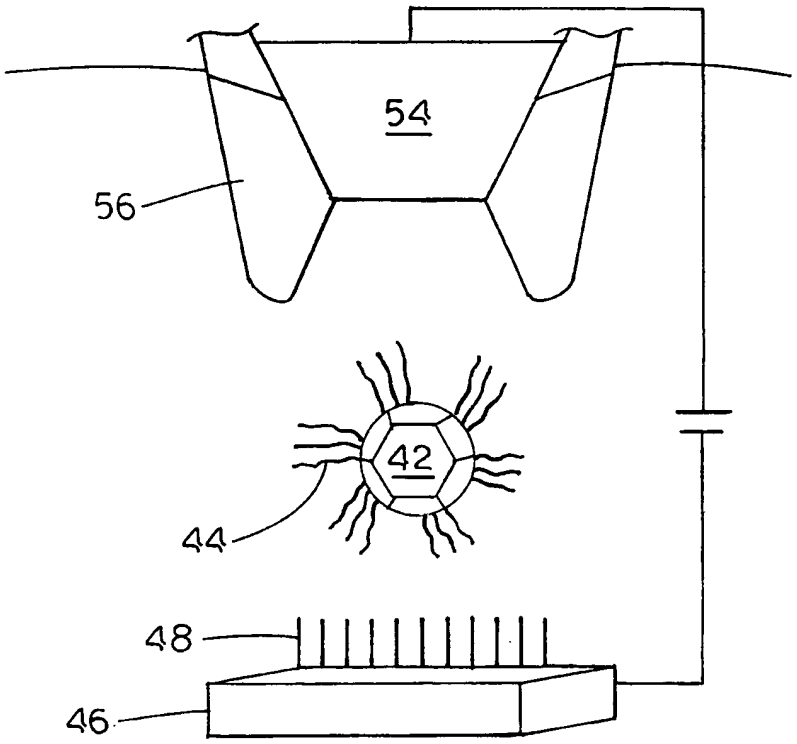

Fig. 5

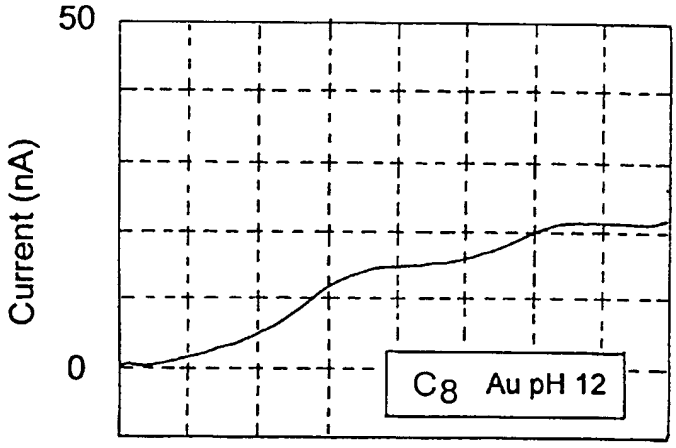

Fig.6A

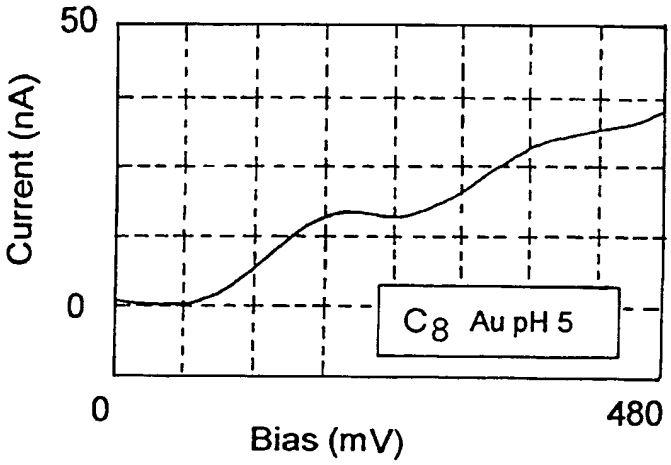

Fig.6B

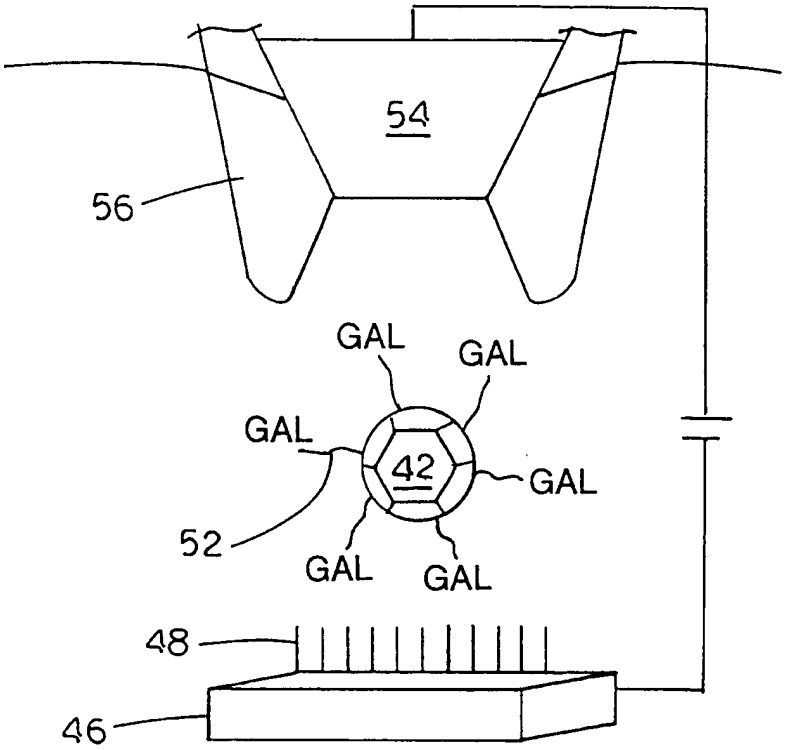

Fig. 7

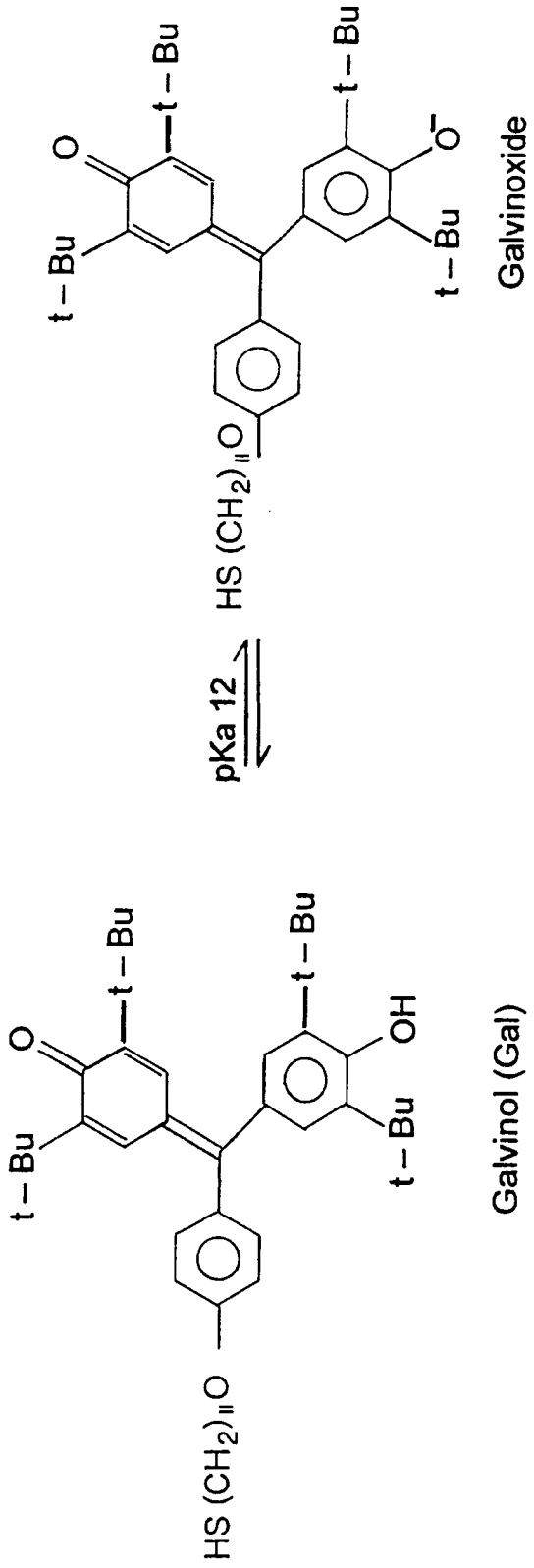
t-Bu
t-Bu
O
t-Bu
t-Bu
O⁻
t-Bu
HS (CH2)11 O
Galvinoxide
pKa 12
t-Bu
t-Bu
O
t-Bu
t-Bu
OH
HS (CH2)11 O
Galvinol (Gal)

Fig.8

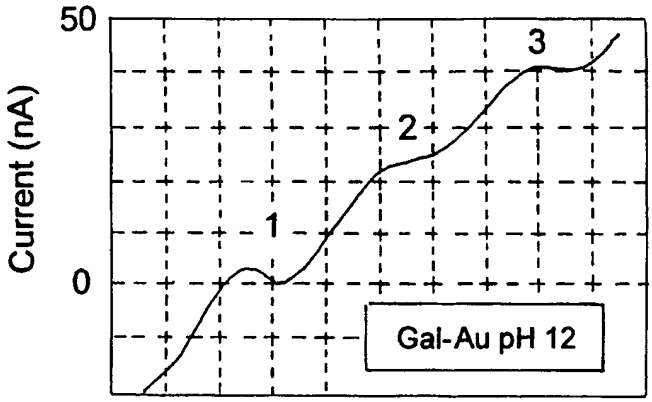

Fig.9A

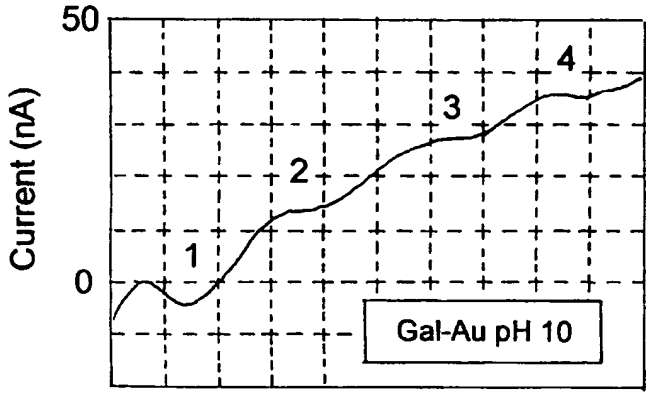

Fig.9B

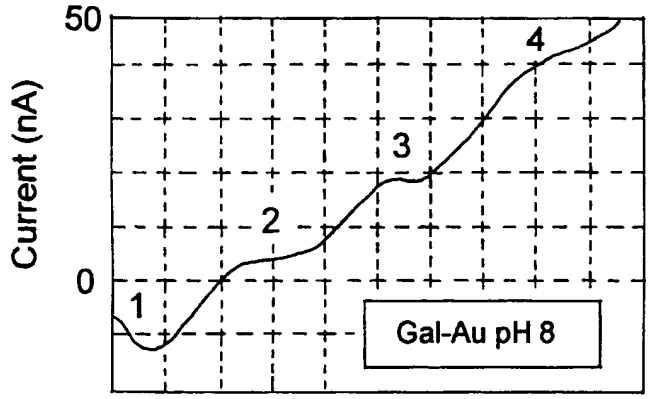

Fig.9C

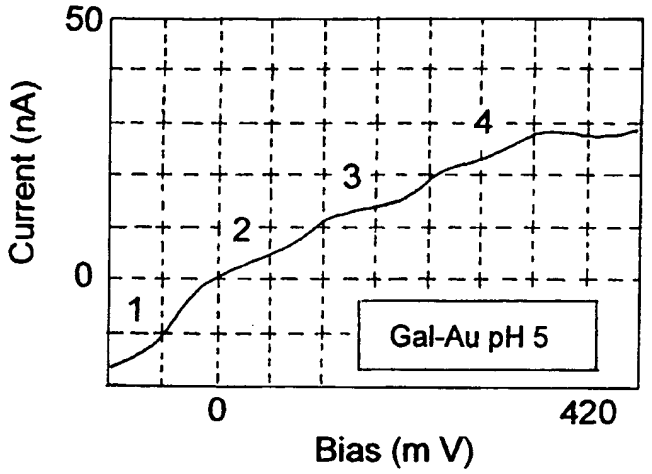

Fig.9D

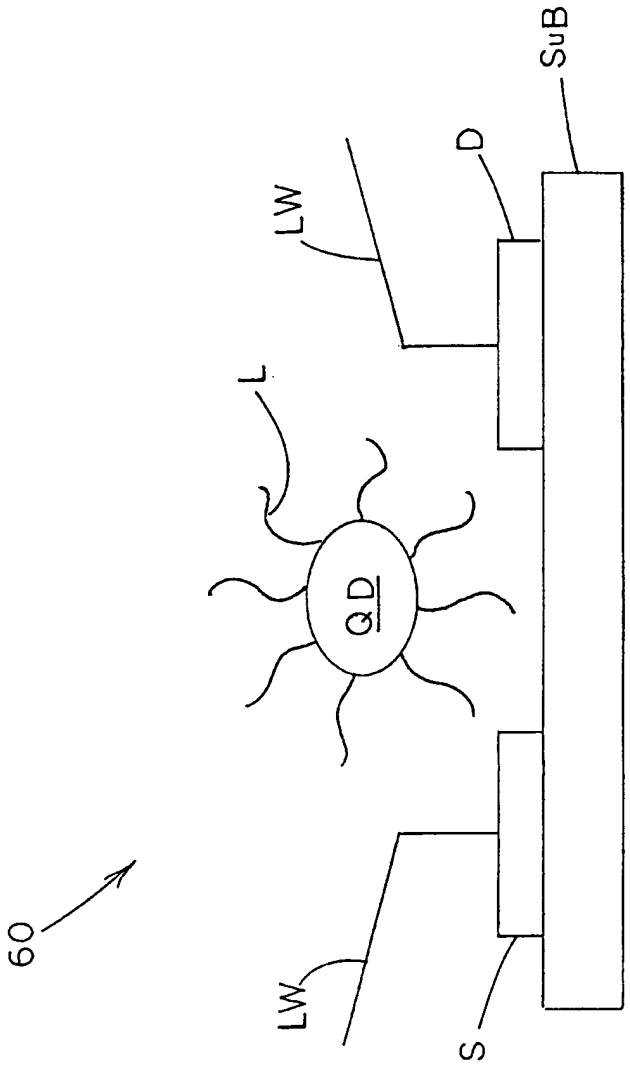

FIG. 10

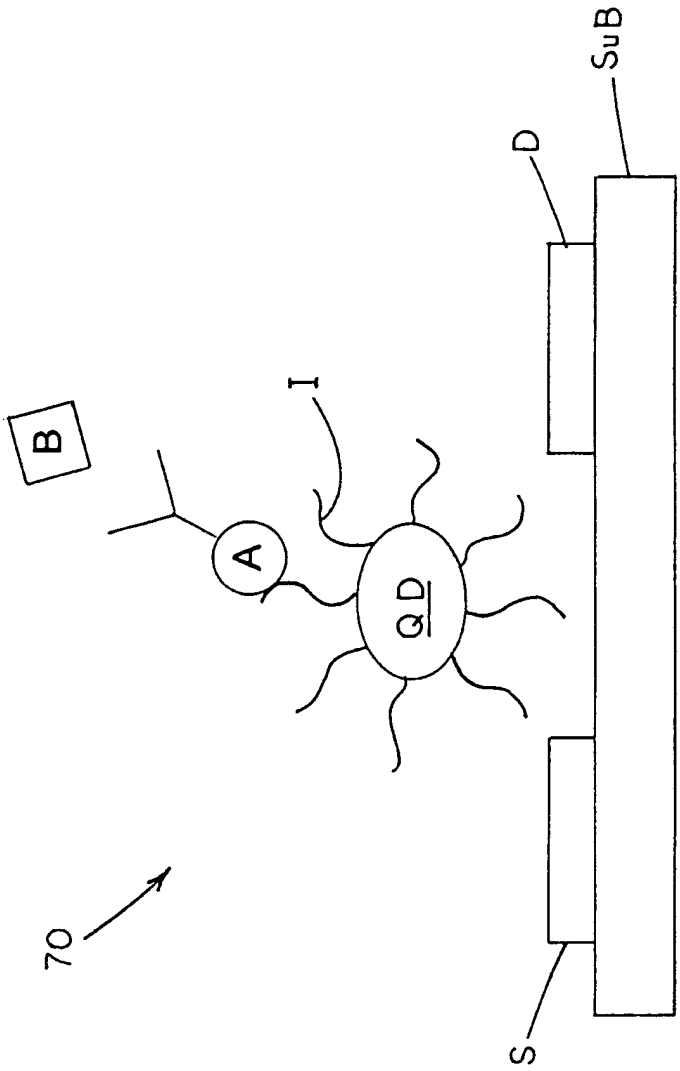

FiG.11

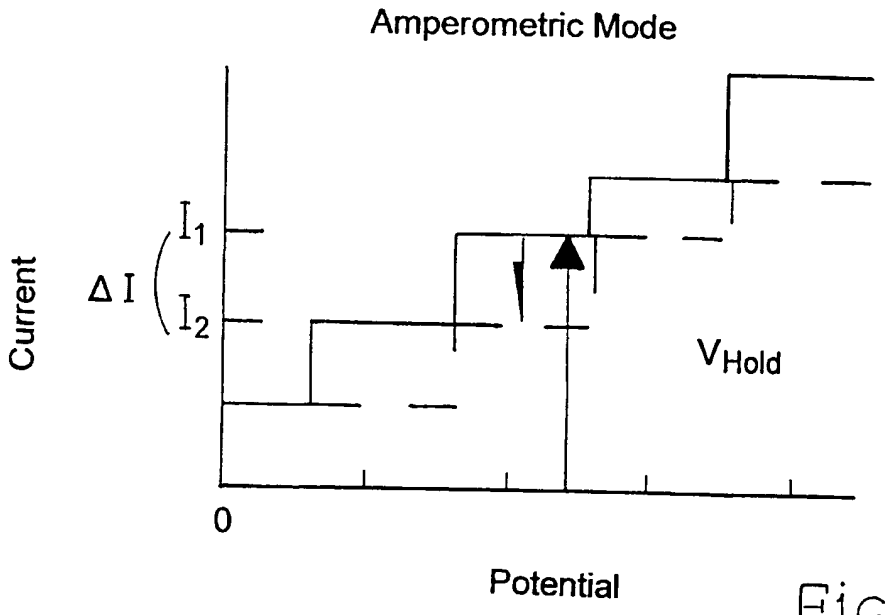

Fig. 12A

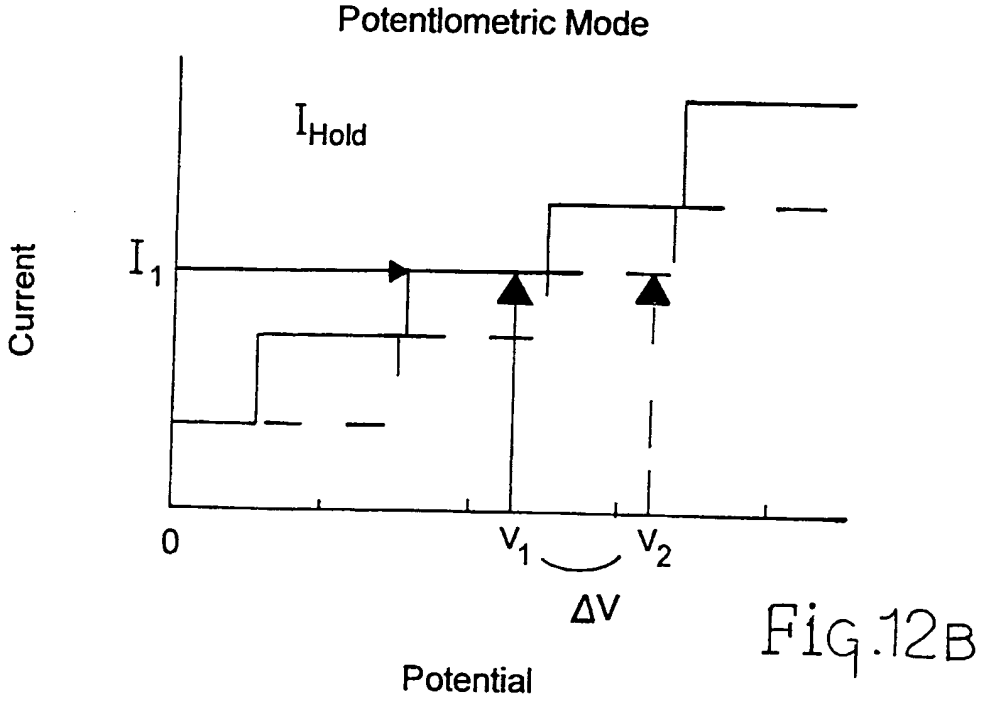

Fig. 12B

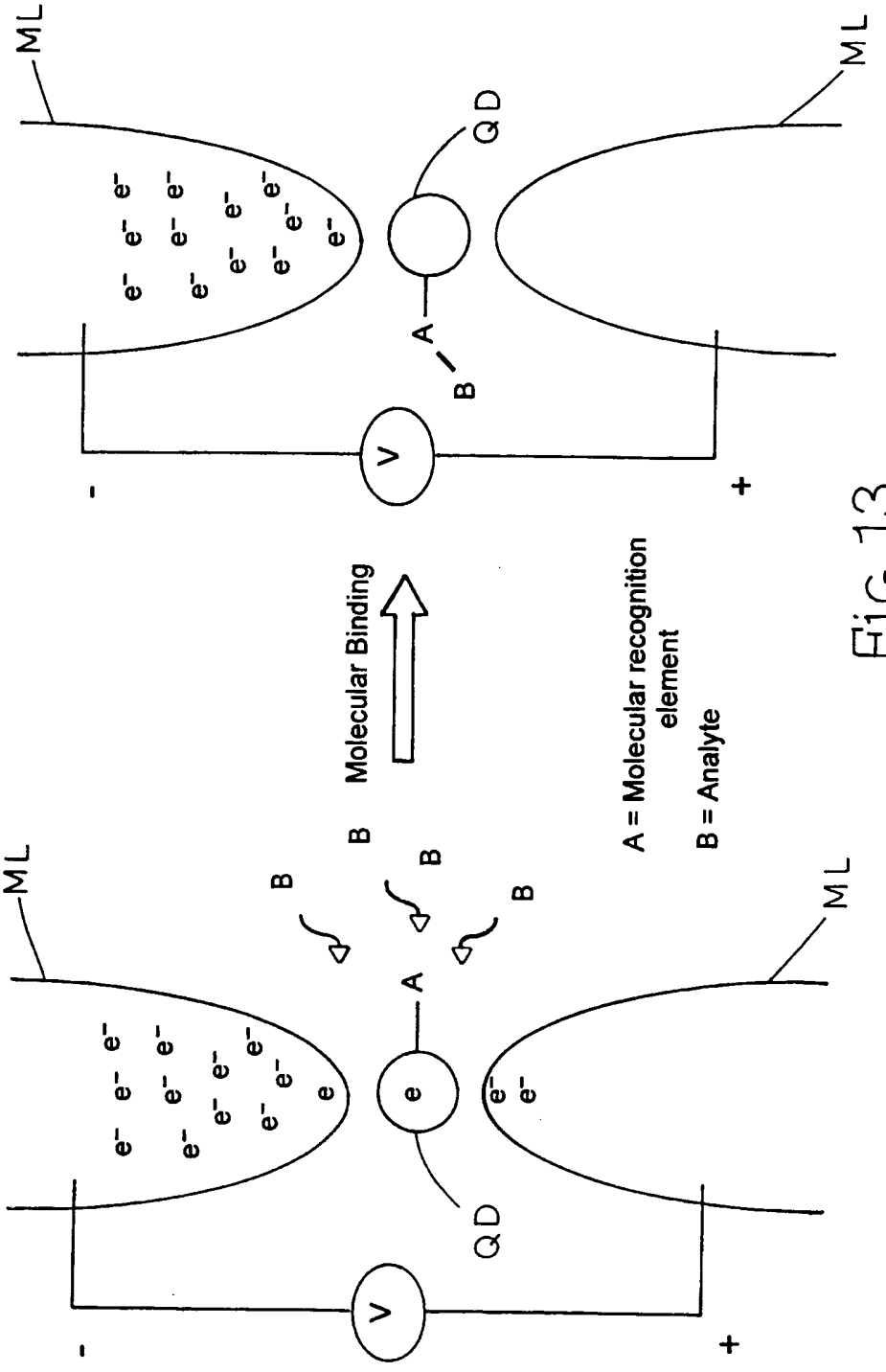
ML
ML
QD
A
B
V
-
+
Molecular Binding
A = Molecular recognition element
B = Analyte
B
B
B
A
QD
e
V
-
+

FIG. 13

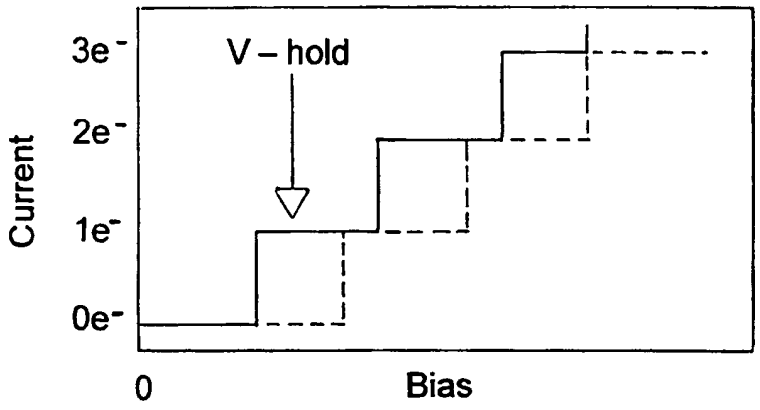

Fig. 14A

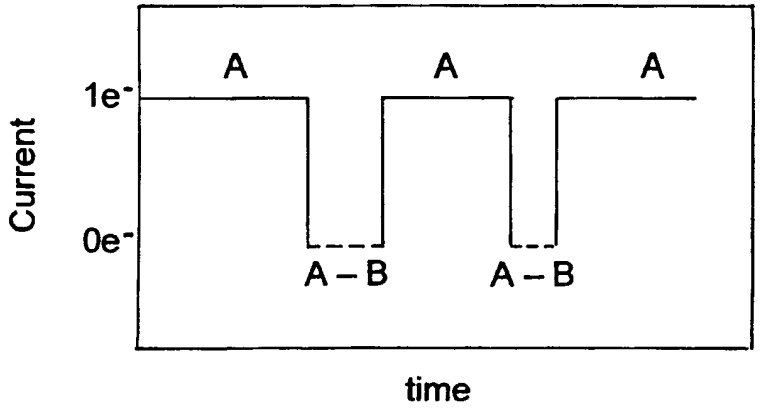

Fig. 14B

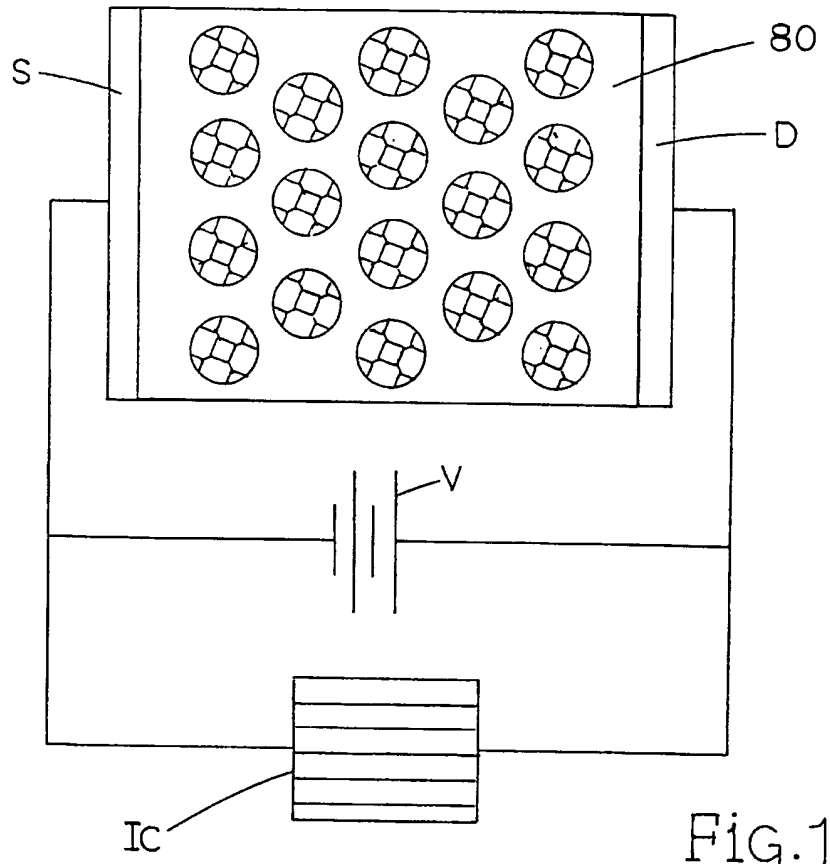

Fig.15

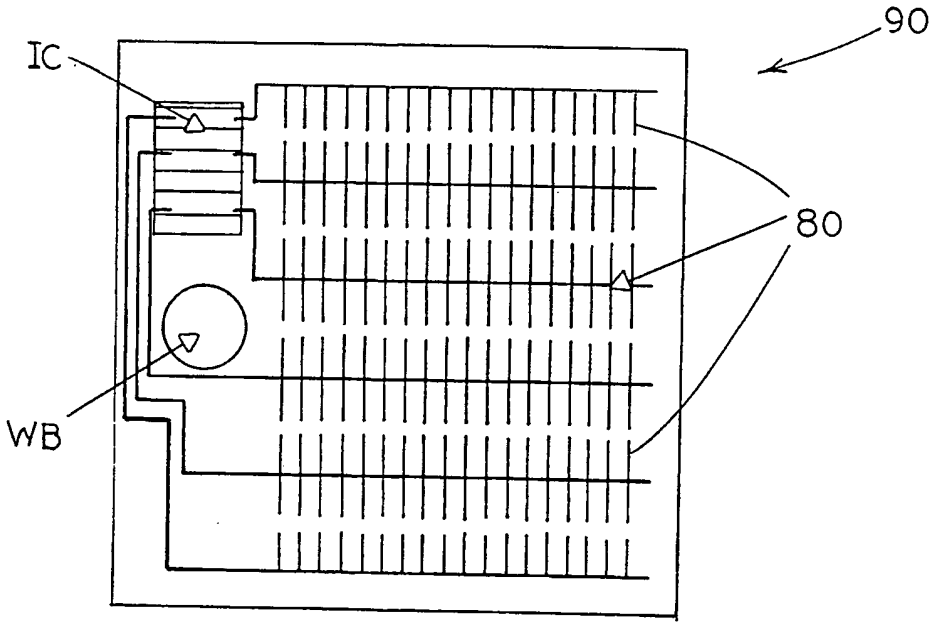

Fig.16

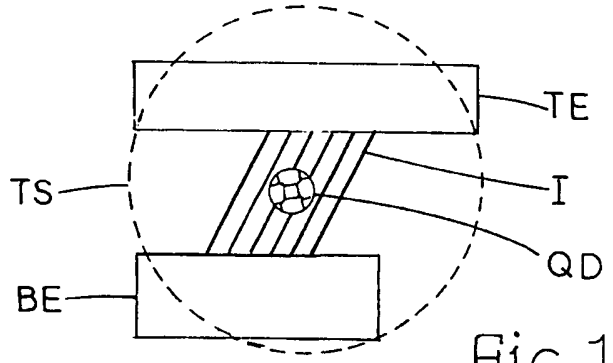

Fig. 17B

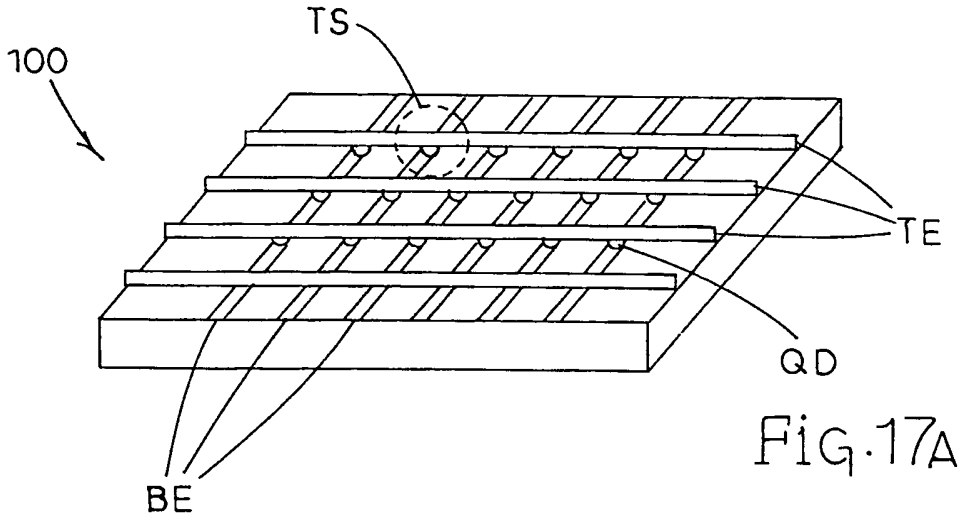

Fig. 17A

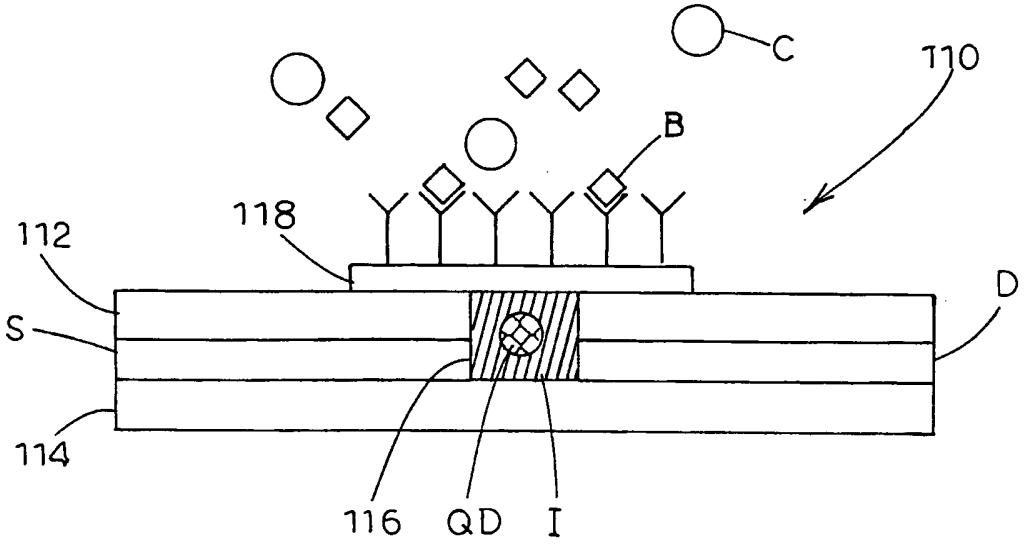

Fig. 18

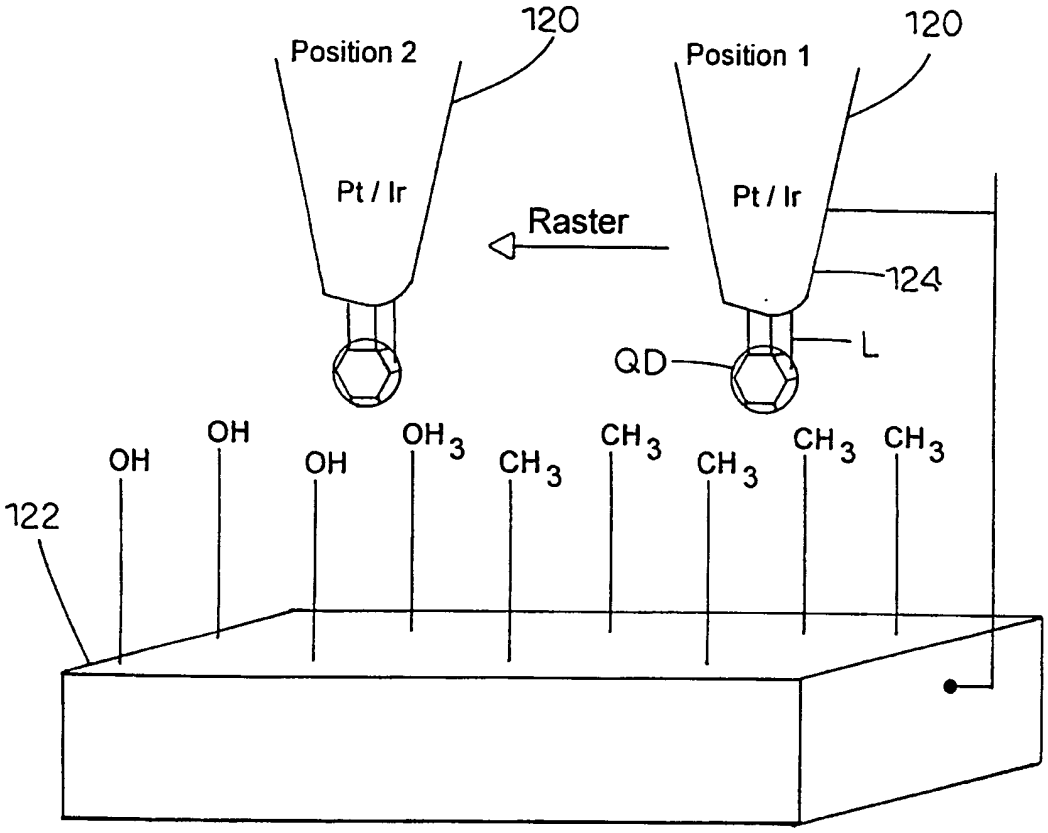
120
Position 2
120
Position 1
Pt / Ir
Raster
Pt / Ir
124
L
QD
OH
OH
OH
OH3
CH3
CH3
CH3
CH3
CH3
122

Fig. 19

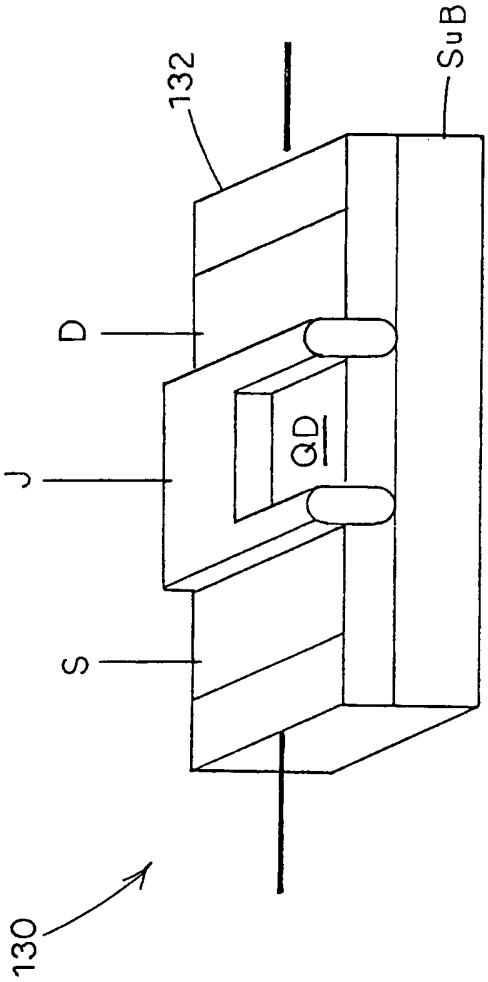

FIG. 20

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/22747

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :H01L 23/58
US CL : 257/253
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 257/253, 20, 24, 30, 39

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

none

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS
search terms: single electron, nanoparticle, current, voltage, source, drain, transistor, analyte

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y --- A,P	FELDHEIM, D. L. et al. Self-assembly of single electron transistors and related devices, Chemical Society Reviews, February 1998, Volume 27, No. 1, pages 1-12, especially Fig. 12 and pages 10-11.	1-17 -------- 18-26
X --- Y	BROUSSEAU, L. C., et al., pH-Gated Single-Electron Tunneling in Chemically Modified Gold Nanoclusters, Journal of the American Chemical Society, August 1998, Volume 120, No. 30, pages 7645-7646, especially Fig. 1.	24 ---- 1-17
Y	US, A, 5,922,537 (EWART ET AL) 13 July 1999 (13/07/99), see figures 1-3, abstract.	1-17

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)		
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed	"&"	document member of the same patent family

Date of the actual completion of the international search 26 NOVEMBER 2000	Date of mailing of the international search report 21 DEC 2000
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer SARA W. CRANE Telephone No. (703) 308-0956

Form PCT/ISA/210 (second sheet) (July 1998)*